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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 487/04, A61K 31/505, C07D 207/34 // (C07D 487/04, 239:00, 209:00)

A1

(11) International Publication Number: WO 94/13676

(43) International Publication Date: 23 June 1994 (23.06.94)

(21) International Application Number: PCT/US93/10715

(22) International Filing Date: 12 November 1993 (12.11.93)

(30) Priority Data:
07/991,764 17 December 1992 (17.12.92) US

(60) Parent Application or Grant
(63) Related by Continuation
US
- Filed on 07/991,764 (CIP)
17 December 1992 (17.12.92)

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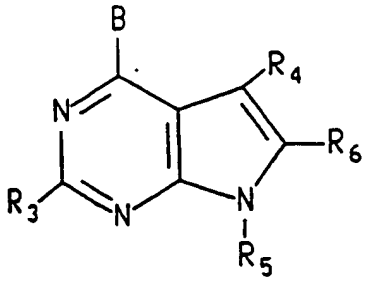
(81) Designated States: AU, BR, CA, CZ, JP, KR, NO, NZ, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: PYRROLOPYRIMIDINES AS CRF ANTAGONISTS

(57) Abstract

The compounds of formula (I), wherein B, R_3, R_4, R_5 and R_6 are as defined herein, are useful in the treatment of stress-related and other diseases. These compounds have corticotropin-releasing factor antagonist activity and as such are of use in the treatment of depression and anxiety related, and other disorders.



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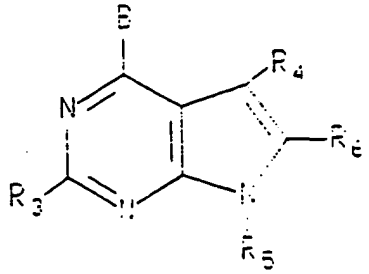
PYRROLOPYRIMIDINES AS CRF ANTAGONISTS

This invention relates to pyrrolopyrimidines, pharmaceutical compositions containing them, and their use in the treatment of stress-related and other diseases. The compounds have corticotropin-releasing factor (CRF) antagonist activity.

CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. The importance of CRF antagonists is set out in the literature, e.g. as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference. A recent outline of the different activities possessed by CRF antagonists is found in M.J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are considered effective in the treatment of a wide range of diseases including stress-related illnesses, such as stress-induced depression, anxiety, and headache; abdominal bowel syndrome; irritable colon syndrome; spastic colon; irritable colon; inflammatory diseases; immune suppression; human immunodeficiency virus (HIV) infections; Alzheimer's disease; gastrointestinal diseases; anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction, and fertility problems.

Certain substituted pyrrolopyrimidines have been described in the prior art. U.S. Patent 4,229,453 describes 4-amino substituted pyrrolopyrimidines for treating CNS illnesses or inflammations. Robins, Can. J. Chem., 55, 1251 (1977) describes the antibiotic tubercidin having a 7-ribofuranosyl group attached to 4-aminopyrrolopyrimidine. German Patent Publication 3145287 refers to three 7-bromophenyl-5,6-dimethyl-pyrrolopyrimidines as having analgesic, sedative, anti-convulsant and anti-inflammatory activity.

The present invention relates to a compound of the formula



and the pharmaceutically acceptable acid addition salts thereof, wherein

B is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, O-C-(C_1-C_6 alkyl), O-C-NH(C_1-C_4 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_6 alkyl), N(C_1-C_4 alkyl)C(C_1-C_4 alkyl), NHC(C_1-C_4 alkyl), COOH, C O(C_1-C_4 alkyl), C NH(C_1-C_4 alkyl), C N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, O-C-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), N(C_1-C_4 alkyl)-C(C_1-C_4 alkyl), NHC(C_1-C_4 alkyl), COOH, C O(C_1-C_4 alkyl), C NH(C_1-C_4 alkyl), C N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-

C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ then R_1 and R_2 taken together with the atom to which they are attached may form a saturated 3- to 8-membered ring of which the 5- to 8-membered ring may contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl or benzyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, $O(C_1$-C_6 alkyl), $NH(C_1$-C_6 alkyl), $N(C_1$-C_4 alkyl)$(C_1$-C_2 alkyl), SH, $S(C_1$-C_4 alkyl), $SO(C_1$-C_4 alkyl), or $SO_2(C_1$-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain one double or triple bond and may be substituted by from 1 to 3 substituents R_5 independently selected from the group consisting of hydroxy, C_1-C_3 alkoxy, fluoro, chloro or C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl$)(C_1$-C_2 alkyl), $SO_n(C_1$-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, NHC(C_1-C_4 alkyl), $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl$)(C_1$-C_2 alkyl), C(O)$O(C_1$-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl$)(C_1$-C_3 alkyl), $COO(C_1$-C_4 alkyl), $CO(C_1$-C_4 alkyl), $SO_2NH(C_1$-C_4 alkyl), $SO_2N(C_1$-C_4 alkyl$)(C_1$-C_3 alkyl), SO_2NH_2, $NHSO_2(C_1$-C_4 alkyl), $S(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), wherein said C_1-C_4 alkyl

and C_1-C_6 alkyl may be substitut d by one or two of fluoro, chloro, hydroxy, C_1-C_4 alkoxy, amino, methylamino, dimethylamino or acetyl wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain one double or triple bond; with the proviso that R_5 is not unsubstituted phenyl;

R_6 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, NHC(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), C(=O)O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_{11} is hydrogen, hydroxy, fluoro, chloro, COO(C_1-C_2 alkyl), cyano, or CO(C_1-C_2 alkyl); and

R_{12} is hydrogen or C_1-C_4 alkyl; with the proviso that (1) B is not straight chain alkyl, (2) when R_5 is unsubstituted cycloalkyl, R_3 and R_4 are hydrogen, and R_6 is hydrogen or methyl, then B is not NHR_2 wherein R_2 is benzyl or thienylmethyl, and (3) when R_5 is p-bromophenyl, and R_3, R_4 and R_6 are methyl, then B is not methylamino or hydroxyethylamino.

Preferred compounds of the formula I of the invention are those wherein B is NR_1R_2, $NHCHR_1R_2$, or $OCHR_1R_2$, wherein R_1 is C_1-C_6 alkyl, which may be substituted by one of hydroxy, fluoro or C_1-C_2 alkoxy, and may contain one double or triple bond; those wherein R_2 is benzyl or C_1-C_6 alkyl which may contain one double or triple bond, wherein said C_1-C_6 alkyl or the phenyl in said benzyl may be substituted by fluoro, C_1-C_6 alkyl, or C_1-C_6 alkoxy; those wherein R_3 is methyl, ethyl, fluoro, chloro or methoxy; those wherein R_4 and R_6 are independently hydrogen, methyl, or ethyl; and those wherein R_5 is phenyl substituted by two or three substituents, said substituent being independently fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl, C_1-C_6 alkyl which may be substituted by one of hydroxy, C_1-C_4 alkoxy or fluoro and may have one double or triple bond, -(C_1-C_2 alkylene)O(C_1-C_2 alkyl), C_1-C_3 hydroxyalkyl, hydroxy, formyl, COO(C_1-C_2 alkyl), -(C_1-C_2 alkylene)amino, or -C(O)(C_1-C_2 alkyl).

Specific pr f rr d compounds include:

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trim thylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;

4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidin-4-yl]amine;

2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;

2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2.3-d]pyrimidin-4-ylamino]-butan-1-ol;

2-(S)-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2.3-d]pyrimidin-4-ylamino]-butan-1-ol;

4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidine;

4-(1-methoxymethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

4-(1-ethyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo-[2.3-d]pyrimidine;

[7-(4-bromo-2.6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2.3-d]pyrimidin-4-yl]-(1-methoxymethyl-propyl)-amine;

2-[7-(2-bromo-4,6-dimethyl-phenyl)-2.5-dimethyl-7H-pyrrolo[2.3-d]pyrimidin-4-ylamino]-butan-1-ol;

2-[7-(4-ethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;

2-[7-(2-ethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol; and

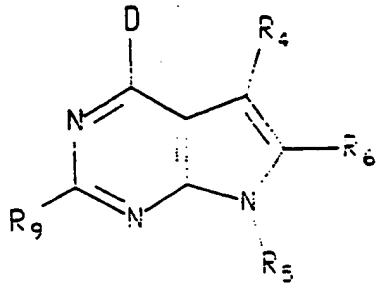
2-[7-(2-fluoromethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol.

The invention also relates to a pharmaceutical composition for the treatment of illnesses induced or facilitated by corticotropin releasing factor which comprises a compound of the formula I as defined above in an amount effective in the treatment of said illnesses, and a pharmaceutically acceptable carrier, and a pharmaceutical composition for the treatment of inflammatory disorders, such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache; pain; cancer; irritabl bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms: drug addiction; stress-induced psychotic episodes; and fertility problems, which comprises a compound of the formula I as defined above in an amount effective in the treatment of said disorders, and a pharmaceutically acceptable carrier. Preferred compositions of the invention are those containing preferred compounds of formula I as described above.

The invention further relates to a method for the treatment of illnesses induced or facilitated by corticotropin releasing factor by administering to a subject in need of such treatment a compound of formula I as defined above in an amount effective in such treatment, and a method for the treatment of inflammatory disorders, such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache: pain: cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal diseases: eating disorders such as anorexia nervosa: hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction: stress-induced psychotic episodes; and fertility problems, particularly depression and anxiety, by administering to a subject in need of such treatment a compound of formula I as defined above in an amount effective in

such treatment. Preferred methods of the invention are thos administering a preferred compound of the formula I as described above.

The invention also relates to an intermediate compound of the formula



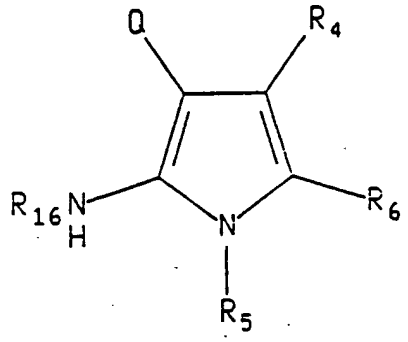
wherein

D is hydroxy, chloro, or cyano,

R_4 and R_6 are each independently hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, $SO_n(C_1$-C_6 alkyl), wherein n is 0, 1 or 2, or cyano, wherein said C_1-C_6 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, $NHC(=O)(C_1$-C_4 alkyl), $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl)$(C_1$-C_2 alkyl), $C(=O)O(C_1$-C_4 alkyl). C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperdinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each of the above groups may be substituted independently by from one to three of fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of bromo, iodo, cyano, nitro, amino, $NH(C_1$-C_4 alkyl), $N(C_1$-$C_4)(C_1$-C_2 alkyl), $COO(C_1$-C_4 alkyl), $CO(C_1$-C_4 alkyl), $SO_2NH(C_1$-C_4 alkyl), $SO_2N(C_1$-C_4 alkyl)$(C_1$-C_2 alkyl), SO_2NH_2, $NHSO_2(C_1$-$C_4)$, $S(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl: and

R_9 is hydrogen, C_1-C_6 alkyl or chloro; with the proviso that when (a) R_4 and R_6 are methyl, R_9 is hydrogen and D is hydroxy, then R_5 is not phenyl (1) substituted by one of halogen, nitro, C_1-C_6 alkyl, C_1-C_6 alkoxy, or trifluoromethyl, and optionally in addition substituted by one or two of halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, or (2) di-or trisubstituted by one of nitro or trifluoromethyl and one or two of halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy, and (b) when D is chloro, R_4 and R_9 are hydrogen, and R_6 is C_1-C_6 alkyl, then R_5 is not unsubstituted cyclohexyl; and a compound of the formula



VII

wherein

Q is $C(O)CHR_1R_2$ or cyano;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, $S(C_1$-C_6 alkyl), or nitro, and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, $S(C_1$-C_6 alkyl), or nitro, and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to thre double or triple bonds; or

R_4 and R_6 are each independently hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, $SO_n(C_1$-C_6 alkyl), wherein n is 0, 1 or 2, cyano, wherein said

C_1-C_6 alkyl may be substituted by one C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of bromo, iodo, cyano, nitro, amino, $NH(C_1$-C_4 alkyl), $N(C_1$-$C_4)(C_1$-C_2 alkyl), $COO(C_1$-C_6 alkyl), $CO(C_1$-C_4 alkyl), $SO_2NH(C_1$-C_6 alkyl), $SO_2N(C_1$-C_4 alkyl)$(C_1$-C_2 alkyl), SO_2NH_2, $NHSO_2(C_1$-C_4 alkyl), $S(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl; and R_{16} is hydrogen or $C(O)C_1$-C_6 alkyl; with the proviso that when Q is cyano, R_4 and R_6 are not both methyl.

Whenever reference is made to alkyl, this includes both straight and branched chain alkyl.

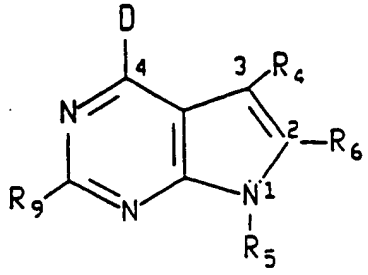
Whenever reference is made herein to 3-to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl containing one to three of O, S or N-Z, it is understood that the oxygen and sulfur ring atoms are not adjacent to each other. The three membered cycloalkyl has just one O, S or N-Z. An example of a six-membered cycloalkyl having O and N is morpholinyl.

Whenever R_2 or R_5 is a heterocyclic group, the attachment of the group is through a carbon atom.

Whenever reference is made herein to C_1-C_4 alkyl or C_1-C_6 alkyl which "may contain one or two double or triple bonds" in the definitions of R_1, R_2 and R_3, it is understood that at least two carbons are present in the alkyl for one double or triple bond, and at least four carbons for two double and triple bonds.

Whenever an alkoxy group, e.g. in the definitions of R_1 and R_2, may have a double or triple bond, it is understood that such double or triple bond is not directly attached to the oxygen.

Th compounds of formula I wh rein B is NR_1R_2, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, or $NHNR_1R_2$, and R_3 is hydrogen, C_1-C_6 alkyl or chloro (hereafter R_3) may be prepared by reaction of a compound of the formula



II

wherein D is Cl, and R_4, R_5 and R_6 are as defined above with reference to formula I, with a compound of the formula BH wherein B is as defined immediately above. The reaction is carried out in a solvent in the presence of a base at a temperature of between about 0° to about 150°C. Suitable solvents are organic solvents such as acetonitrile, dimethylsulfoxide, acetone, C_2-C_{15} alkyl alcohol, tetrahydrofuran, chloroform, benzene, xylene or toluene, preferably acetontrile or dimethylsulfoxide.

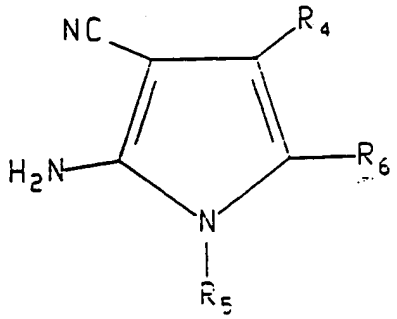
When B is NR_1R_2, $NHNR_1R_2$, or $NHCR_1R_2R_{11}$, an excess of BH is used. Other bases such as potassium carbonate or tri-(C_1-C_6)alkyl amine may be used instead. The reaction is carried out at a temperature of about 75° to 150°C. When the reaction is carried out in the presence of a base, such as sodium hydride or potassium C_1-C_2 alkoxide, a molar equivalent of the amine is used. When B is $OCR_1R_2R_{11}$ or $SCR_1R_2R_{11}$, a base which is capable of deprotonation of BH may be used, such as an alkali metal hydride such as sodium or potassium hydride, or an organometallic base such as sodium diisopropylamide, sodium bis(trimethylsily)amide, lithium diisopropylamide, lithium bis(trimethylsily)amide, sodium C_1-C_4 alkoxide or n-butylithium. The solvent used is dry tetrahydrofuran, dimethylsulfoxide, methylene chloride, or toluene, and the reaction temperature is between about -78°C and the reflux temperature of the reaction mixture, preferably 0°C to 80°C.

The compounds of formula I wherein R_2 is the groups other than R_3 (hereafter R_{10}) may be prepared by r acting a compound of the formula I wherein R_2 is chloro with a nucleophile of the formula $R_{10}H$ with or without an organic or inorganic base. Suitable bases include sodium, sodium hydride, and alkali metal hydroxide such as potassium hydroxide, and weaker bases such as potassium carbonate or triethylamine.

The latter are generally used when $R_{10}H$ is alkanol, C_1-C_6 alkanethiol, an amine, .g. $NH(C_1$-C_6 alkyl), or tetrahydrobutyl ammonium fluoride. Suitable solvents are dimethylsulfoxide, acetonitrile, C_1-C_5 alkyl alcohol, tetrahydrofuran, benzene, toluene or methylene chloride.

The compounds of formula II wherein D is chloro may be prepared by reacting the corresponding 4-hydroxy compound of formula III (not shown) with an excess of phosphorus oxychloride or thionyl chloride at temperatures between about 60 to 140°C, conveniently at the reflux temperature of the reaction mixture. When the reaction is carried out in a solvent, suitable solvents are halogenated alkanes. such as methylene chloride or chloroform. The reaction may be in the presence of a base such as N,N-diethylaniline, trimethylamine or potassium carbonate.

The compounds of formula III wherein R_9 is hydrogen may be prepared by reaction of a compound of the formula



IV

wherein R_4, R_5, and R_6 are as defined with reference to formula I with formic acid at a temperature between about 60 to 140°C, preferably at the reflux temperature of the reaction mixture.

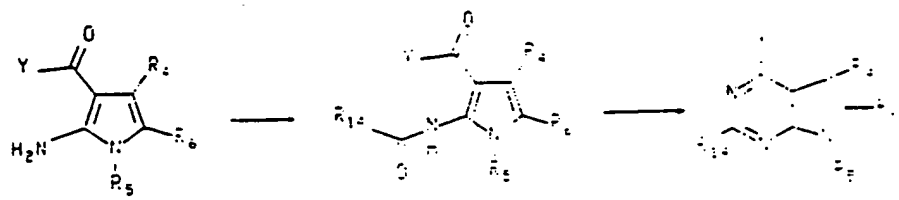
The compounds of formula III wherein R_9 is C_1-C_6 alkyl (hereafter R_{13}) may be prepared by reacting a compound of formula IV with $R_{13}COOCOR_{13}$ in $R_{13}COOH$ or $R_{13}CO(OC_1$-C_2 alkyl)$_3$ in acetic acid or an appropriate organic solvent such as ethyl acetate or toluene, at a temperature between 25° to 120°C, preferably at the reflux temperature of the reaction mixture. The compounds of formula III wnerein R_9 is hydroxy may be prepared by reacting a compound of formula IV with chlorosulfonyl isocyanate in an appropriate solvent at temperature between -78°C to 100°C. preferably at -20°C to 60°C, followed by acid hydrolysis. The appropriate solvents include methylene chloride. dimethyl formamide. tetrahydrofuran. and toluene.

preferably dimethyl formamide or methylene chloride. The above formed compounds wherein R_9 is hydrogen, C_1-C_6 alkyl or hydroxy may be heated in aqueous acid to give the compounds of formula III. The appropriate aqueous acids are 85% phosphoric acid, hydrochloric acid, sulfuric acid, or acetic acid, preferably 85% phosphoric acid. The reaction is generally carried out at about 25 to 150°C, preferably 80 to 130°C. Alternatively, the formed compounds may be heated with phosphorous pentoxide and N,N-dimethylcyclohexanamine at about 150 to 200°C.

The compounds of formula IV may be prepared by conventional methods.

The compounds of formula I wherein B is $CR_1R_2R_{11}$ and R_3 is hydrogen. C_1-C_5 alkyl, or hydroxy (hereafter R_{14}) may be prepared, as depicted in Scheme 1, by heating a compound of the formula VI, wherein R_{14} is hydrogen, C_1-C_6 alkyl or amino, R_1, R_2, R_{11}, R_4, R_5, and R_6 are as defined above, and Y is $CR_1R_2R_{11}$, with ammonium chloride and $R_{14}CONH_2$ at reflux temperatures.

Scheme 1



V

The compounds of formula I wherein B is $CR_1R_2R_{11}$, as defined above with reference to formula I and R_3 is as defined above with reference to formula I, other than hydrogen, C_1-C_6 alkyl, or hydroxy, may be prepared by reacting the 2-chloro derivatives of formula I wherein R_3 is chloro (formula I-B, not shown) with a nucleophile of formula $R_{15}H$ with or without an organic or inorganic base by the method described pr viously for the reaction with $R_{10}H$, wherein R_{15} is R_3 other than hydrogen, C_1-C_6 alkyl, hydroxy, and chloro. The compounds of formula I-B may be prepared by a method analogous to that for the conversion of compounds III to compounds II wherein D is chloro.

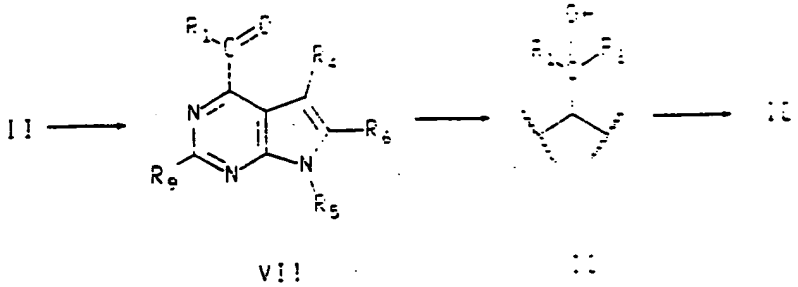
Th compounds of formula VI may be prepared, as shown in Scheme I, starting from compounds of the formula V by methods analogous to those for tne conversion of compounds IV to compounds III.

The compounds of formula V may be prepared by methods analogous to the conventional methods used for the preparation of compounds of formula IV by using $YCOCH_2CN$ instead of malonitrile, wherein Y is $CR_1R_2R_{11}$.

The compounds of formula I wherein B is $C(O)R_2$ may be prepared by reacting a compound of formula II wherein D is cyano with a Grignard reagent containing group R_2, e.g. R_2MgCl, or R_2MgBr.

The compounds of formula I wherein B is $CR_1R_2R_{11}$, $C(C=CR_2R_{12})R_1$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$, and R_3 is R_9 as defined above with reference to formula II, may be prepared as depicted in Scheme 2.

Scheme 2



The compounds of formula II wherein D is cyano and R_4, R_5, R_6 and R_9 are as defined above, prepared by reacting the corresponding compound wherein D is chloro with potassium cyanide in dimethylsulfoxide, are reacted with a Grignard reagent containing group R_1 as defined above to form the compound of formula VII. Further reaction of the compound of formula VII with a Grignard reagent containing group R_2 as defined above provides the compound of formula IC. Corresponding compounds of formula ID wherein B is $CR_1R_2R_{11}$ or $C(=CR_1R_{12})R_1$ may be prepared by conventional methods. Thus, reaction of IC with an acid, such as concentrated sulfuric acid or hydrochloric acid, gives a compound of formula I wherein B is $C(=CR_2R_{12})R_1$. Hydrogenation of a compound wherein B is $C(=CR_2R_{12})R_1$ using Pd/C or platinum oxide catalyst gives a compound I wherein B is CHR_1R_2. Reaction of a compound I wherein B is CR_1R_2OH with diethylamino sulfur trifluoride or triphenylphosphine carbontetrachloride affords a compound I wherein B is CR_1R_2F or CR_1R_2Cl, respectively.

When the compounds of the invention contain one or more chiral centers, it is understood that the invention includes the racemic mixture and the individual diastereomers and enantiomers of such compounds.

The acid addition salts of the compounds of formula I are prepared in a conventional manner by treating a solution or suspension of the free base of formula I with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques are employed in isolating the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, mandelic, di-p-toluoyl-L-tartaric and related acids.

The novel compound of the invention of formula I may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple, e.g. up to three, doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of formula I and the pharmaceutically acceptable carriers are then readily administered in a vari ty of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of ral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of the novel compound of formula I in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rend red isotonic with sufficient saline or glucose. These particular

aqueous solutions ar. especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Additionally, it is possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may be don by way of creams, jellies, gels, pastes and ointments in accordance with standard pharmaceutical practice.

The effective dosage for the compound of formula I depends on the intended route of administration and other factors such as age and weight of the patient, as generally known to a physician. The dosage also depends on the illness to be treated. The daily dosage will generally range from about 0.1 to 50 mg/kg of the body weight of the patient to be treated. For treatment of inflammatory diseases about 0.1 to about 100 mg/kg will be needed, for Alzheimer's disease, about 0.1 to about 50 mg/kg, as well as for gastrointestinal diseases, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, etc.

The methods for testing the compounds for formula I for their CRF antagonist activity are according to the procedures of Endocrinology, 116, 1653-1659 (1985) and Peptides, 10, 179-188 (1985) which determine the binding affinity of a test compound for a CRF receptor. The binding affinities for the compounds of formula I, expressed as IC_{50} values, generally range from about 0.2 nanomolar to about 10 micromolar.

The following Examples illustrate the invention. The following abbreviations are used: Ph=phenyl, Me=methyl, Bu=butyl, Et=ethyl, Pr=propyl.

Example 1

A. 2-amino-4-methyl-1-(2,4,6-trimethylphenyl)pyrrole-3-carbonitrile

A mixture 2-(2-bromo-1-methyl-ethylidene)-malononitrile and 2,4,6-trimethylaniline (17.330 g, 91.24 mmol) in 40 mL of isopropanol was stirred at room temperature for 15 hours. The reaction mixture was concentrated to dryness and diluted with chloroform and water. The chloroform layer was neutralized with dilute sodium hydroxide and washed with brine, separated, dried and concentrated to give 33.000 g of brown oily solid. The solid was purified through silica gel column chromatography to give 9.35 g (47.5%) of the title compound as an orange-yellow solid. ^1H NMR ($CDCl_3$) δ 2.0(s,6H), 2.15(s,3H), 2.35(s,3H), 3.75(brs,2H), 5.8(s,1H), 6.95(s,2H) ppm.

B. N-[3-cyano-4-methyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide

A mixture of the purified compound of step A (3.000 g, 12.54 mmol) and acetic anhydride (1.410 g, 1.31 ml, 13.82 mmol) in 3 ml of acetic acid was refluxed for 45 minutes, cooled and poured onto crushed ice and extracted with ethyl acetate. The organic layer was neutralized, dried and concentrated to give 3.71 g (105%) of dark-pink glass foam. ^{1}H NMR ($CDCl_3$) δ 1.95(s,6H), 2.2(s,3H), 2.32 (s,3H), 6.2(s,1H), 6.8(brs, 1H, NH), 6.9(s,2H) ppm.

C. 2,5-dimethyl-7-(2,4,6-trimethylphenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one

A suspension of the compound of step B (3.200 g, 11.38 mmol) in 3 ml of 85% phosphoric acid was immersed in an oil bath preheated to 130°C for 30 minutes. The reaction mixtures was cooled and poured onto crushed ice and stirred until solid formed and ice melted. The solid was filtered, washed with water to give a tannished solid, the title compound, which was purified through silica gel column chromatography to give a tan solid. ^{1}H NMR ($CDCl_3$) δ 1.92(s,6H), 2.32(s,3H), 2.41(s,3H), 2.45(s,3H), 2.46(s,3H), 6.42(d,1H), 6.95(s,2H) ppm.

D. 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo-[2,3-d]pyrimidine

A mixture of the compound of step C (1.030 g, 3.67 mmol) and $POCl_3$ (3 ml) was heated at reflux for 2.5 hours and cooled. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with dilute sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated to dryness to give the title compound as a tan solid which was purified through silica gel to give an off-white solid. ^{1}H NMR ($CDCl_3$) δ 1.90(s,6H), 2.35(s,3H), 2.50(s,3H), 2.65(s,3H), 6.78(s,1H), 7.00(s,2H) ppm.

EXAMPLE 2

A. 2-amino-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrole-3-carbonitrile

A mixture of 3-hydroxy-2-butanone (100.000 g, 1.135 mol), 2,4,6-trimethylaniline (153.225 g, 1.135 mol) and p-toluenesulfonic acid (0.670 g) in 500 ml of benzene was refluxed using a Dean-Stark trap to remove water. After 2 hours,malononitrile (75.000 g, 1.135 mol) was add d and the mixture was refluxed for an additional 10 hours until all the staring material was consumed. The reaction mixture was cooled and precipitate formed and filtered. The solid was washed with a minimum amount of ethanol. The

solid was diluted with 500 ml of benzene and product was dissolved. Some undesired product was insoluble and was filtered off. The filtrate was concentrated to give a tan solid which was recrystallized from ethanol to give 130.260 g of off-white crystals. ^{1}H NMR ($CDCl_3$) δ 1.68(s,3H), 1.93(s,6H), 2.05(s,3H), 2.31(s,3H), 3.62(brs,2H), 6.95(s,2H) ppm.

B. N-[3-cyano-4,5-dimethyl-1-(2,4,6-trimethyphenyl)-1H-pyrrol-2-yl]-acetamide

The title compound was prepared as a tan solid by the procedure analogous to that of Example 1A starting with the compound of step A and acetic anahydride in acetic acid. The crude material was pure and used directly for the next cyclization step. ^{1}H NMR ($CDCl_3$) δ 1.75(s,3H), 1.80(s.6H), 1.95(s,3H), 2.18(s,3H), 2.30(s,3H). 6.60(brs. 1H), 6.93(s,2H) ppm.

C. 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-3,7-dihydro-pyrrol[2,3-d]pyrimidin-4-one

A mixture of the compound of step B(157.600 g, 0.53 mol) and 100 ml of 85% phosphoric acid was heated for 0.5 hours in an oil bath at a temperature of 130°C. All the starting material was consumed and the desired product formed. The mixture was cooled, poured into 1200 ml of ice-water, and stirred. Precipitate formed and was filtered. The solid was washed with water, dried overnight to give 113.220 g of the title compound as brick-pink solid. ^{1}H NMR ($CDCl_3$) δ 1.85(s.6H). 1.87(s,3H), 2.34(s.3H). 2,41(s,3H), 2.44(s,3H), 7.00(s,2H) ppm.

EXAMPLE 3

A. 2-amino-4,5-diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrole-3-carbonitrile

The crude material of the title compound was prepared as an oil by the procedure analogous to that of Example 2A starting with 4-hydroxy-3-hexanone. The crude material was used directly for the next acetylation step without further purification.

B. N-[3-cyano-4,5-diethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide

The title compound was prepared as an oil by the procedure of Example 1A starting with the compound of above step A and acetic anhydride in acetic acid. The crude material was purified through silica gel column chromatography using chloroform as eluent to give the title compound as an oil. ^{1}H NMR ($CDCl_3$) δ 0.85(t.3H), 1.26(t.3H). 1.92(s,6H), 2.19(s,3H). 2.23(q.2H), 2.33(s,3H). 2.59(q.2H). 6.95(s.2H) ppm.

C. 2-methyl-5,6-diethyl-7-(2,4,6-trimethylphenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one

The title compound was prepared as a brown solid by the procedure of Example 2C starting with the compound of above step B and 85% phosphoric acid. The crude material was used directly for the next chlorination reaction without further purification.

EXAMPLE 4

The following compounds were prepared according to the method of Example 1 starting from the corresponding 2,5,6-trialkyl-7-(2,4,6-trimethylphenyl)-3,7-dihydro-pyrrolo[2,3-d]pyrimidin-4-one.

4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine - a tan solid. ^{1}H NMR ($CDCl_3$) δ 1.81(s,6H), 1.99(s,3H), 2.35(s,3H), 2.46(s,3H), 2.59(s,3H), 7.01(s,2H) ppm.

4-chloro-2-methyl-5,6-diethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin - a tan solid. ^{1}H NMR ($CDCl_3$) δ 0.96(t,3H), 1.31(t,3H), 1.85(s,6H), 2.38(s,3H), 2.46(q,2H), 2.62(s,3H), 2.62(s,2H), 2.92(q,2H), 7.02(s,2H) ppm.

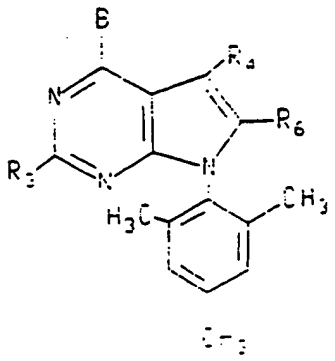
EXAMPLE 5

Butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine

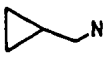
A mixture of 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine (1.000 g, 3.36 mmol) and N-ethylbutylamine (3.400 g, 33.60 mmol) in 5 ml of dimethylsulfoxide was heated to reflux for 1.5 hours. The mixture was cooled and treated with water and a few drops of 2 N HCl to pH 6.5 and extracted with ethyl acetate. The organic layer was separated, washed with dilute sodium bicarbonate, brine, and dried over sodium sulfate anhydrous and concentrated to dryness. The residue was purified through silica gel column chromatography to give 995 mg (81% yield) of the title compound as an oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (t,3H), 1.23(t,3H), 1.35(m,2H), 1.60-1.70(m,2H), 1.92(s,6H), 2.30(s,3H), 2.40(s,3H), 2.46(s,3H), 3.58(t,2H), 3.66(q,2H), 6.55(s,1H), 6.95(s,2H) ppm. The corresponding hydrogen chloride salt was prepared as a white crystals after recrystallization from ethyl acetate. ^{1}H NMR (D_2O) δ 0.90(t,3H), 1.34(m,5H), 1.75(m,2H), 1.90(s,6H), 2.37(s,3H), 2.48(s,3H), 2.55(s,3H), 3.80-3.94(m,4H), 7.09(s,2H) ppm.

EXAMPLE 6

The following compounds were prepared starting with the appropriate amine and the appropriate 4-chloro-2,5,6-trialkyl-7-(substituted phenyl)-7H-pyrrolo[2,3-d]pyrimidine and employing the general procedure of Example 5.



B	R_3	R_4	R_6	^{1}H NMR ($CDCl_3$) δ (ppm)
NMe_2	Me	Me	Me	1.82(s,6H), 2.00(s,3H) 2.38(s,3H) 2.40(s,3H), 2.90(s,3H), 3.58(s,6H), 7.03(s,2H)
NEt_2	Me	Me	Me	1.22(t,6H), 1.84(s,6H), 1.94(s,3H), 2.35(s,3H), 2.38(s,3H), 2.55(s,3H), 3.60(q,4H), 6.98(s,2H)
$N(n\text{-}Pr)_2$	Me	Me	Me	0.90(t,6H), 1.68(q,4H), 1.85(s,6H), 1.95(s,3H), 2.35(s,3H), 2.39(s,3H), 2.48(s,3H), 3.53(q,4H), 6.99(s,2H)
$N\text{-}(n\text{-}Bu)_2$	Me	Me	Me	0.88(t,6H), 1.30(m,4H), 1.61(m,4H), 1.82(s,6H), 1.92(s,3H), 2.30(s,3H), 2.34(s,3H), 2.47(s,3H), 3.50(t,4H), 6.95(s,2H)
EtN(n-Pr)	Me	Me	Me	0.92(t,3H), 1.20(t,3H), 1.64(m,2H), 1.85(s,6H), 1.94(s,3H), 2.35(s,3H), 2.38(s,3H), 2.47(s,3H), 3.49(t,2H), 3.59(q,2H), 6.99(s,2H)
EtN(n-Bu)	Me	Me	Me	0.90(t,3H), 1.19(t,3H), 1.33(m,2H), 1.60(m,2H), 1.83(s,6H), 1.92(s,3H), 2.33(s,3H), 2.35(s,3H), 2.45(s,3H), 3.51(t,2H), 3.58(q,2H), 6.96(s,2H)

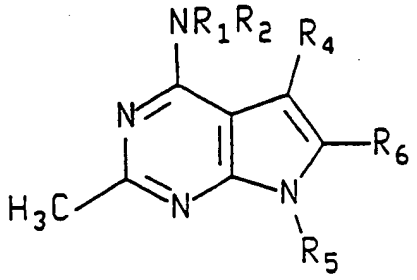
B	R_3	R_4	R_5	^{1}H NMR ($CDCl_3$) δ (ppm)
$EtN(CH_2)_2OH$	Me	Me	Me	1.25(t,3H), 1.78(s,6H), 1.90(s,3H), 2.30(s,3H), 2.36(s,3H), 2.40(s,3H), 3.64(q,2H), 3.75(m,2H), 3.86(t,2H), 6.96(s,2H)
$(n\text{-}Bu)N(CH_2)_2OH$	Me	Me	Me	0.95(t,3H), 1.35(m,2H), 1.71(m,2H), 1.81(s,6H), 1.92(s,3H), 2.31(s,3H), 2.37(s,3H), 2.44(s,3H), 3.55(dd,2H), 3.72(t,2H), 3.87(t,2H), 6.95(s,2H)
$MeN(CH_2CHMe_2)$	Me	Me	Me	0.89(s,3H), 0.91(s,3H), 1.81(s,6H), 1.91(s,3H), 1.96-2.10(m,1H), 2.32(s,3H), 2.35(s,3H), 2.43(s,3H); 3.11(s,3H), 3.32(d,2H), 6.95(s,2H)
	Me	Me	Me	0.35(dd,2H), 0.47(m,2H), 0.90(t,3H), 1.10(m,1H), 1.67(m,2H), 1.83(s,6H), 1.93(s,3H), 2.33(s,3H), 2.37(s,3H), 2.45(s,3H), 3.41(d,2H), 3.62(t,2H), 6.97(s,2H)
$N(CH_2CH{=}CH)_2$	Me	Me	Me	1.85(s,6H), 1.96(s,3H), 2.36(s,3H), 2.39(s,3H), 2.49(s,3H), 4.18(d,4H), 5.20-5.32(m,4H), 5.90-6.10(m,2H), 7.00(s,2H)
MeN-CHMe(Et)	Me	Me	Me	0.87(t,3H), 1.29(d,3H), 1.4.-1.8(m,3H), 1.82(s,3H). 1.86(s.3H), 1.95(s,3H), 2.35(s,3H), 2.37(s.3H), 2.47(s,3H), 3.02(s,3H), 4.34(m,1H), 6.99(s,2H)
$N(CH_2CH_2OH)_2$	Me	Me	Me	1.59(brs,2H), 1.81(s,6H), 1.94(s,3H), 2.34(s,3H), 2.39(s,3H), 3.80-3.95(m,8H), 6.98(s,2H)
$HO(CH_2)_3N(CH_2)_2OH$	Me	Me	Me	1.80(s,6H), 1.93(s,3H), 1.90-2.00(m,2H), 2.33(s,3H), 2.39(s,3H), 2.43(s,3H), 3.65(t,2H). 3.70-3.85(m,2H). 3.89(m,2H). 6.98(s.2H)
$(n\text{-}Bu)N(CH_2CH_2OMe)$	Me	Me	H	0.91(t,3H), 1.31(m,2H). 1.67(m,2H), 1.90(s,6H), 2.32(s,3H), 2.41(s,3H), 2.42(s,3H), 3.36(s,3H), 3.60-3.70(m,4H), 3.82(t,2H). 6.56(s,1H). 6.95(s.2H)

B	R_3	R_4	R_6	^{1}H NMR ($CDCl_3$) δ (ppm)
p-Me-PhCH$_2$N(CH$_2$)$_3$OH	Me	Me	H	1.80(m,2H), 1.90(s,6H), 2.20(s,3H), 2.30(s,3H), 2.34(s,3H), 2.49(s,3H), 3.54(t,2H), 3.82(t,2H), 4.90(s,2H), 6.58(s,1H), 6.95(s,2H), 7.10-7.25(m,4H)
EtN(n-Pr)	Me	Et	Et	0.93(t,6H), 1.1-1.3(m,6H), 1.68(m,2H), 1.88(s,6H), 2.36(s,3H), 2.42(q,2H), 2.49(s,3H), 2.80(q,2H), 3.49(t,2H), 3.58(q,2H), 6.99(s,2H)
EtN(n-Bu)	H	Me	Me	0.91(t,3H), 1.23(t,3H), 1.30(m,2H), 1.62(m,2H), 1.89(s,6H), 2.30(s,3H), 2.44(s,3H), 3.58(t,2H), 3.65(q,2H), 6.67(s,1H), 6.95(s,2H), 8.29(s,1H)
EtN(n-Pr) (HCl salt)	Me	Me	H	0.93(t,3H), 1.25(t,3H), 1.70(m,2H), 1.91(s,6H), 2.33(s,3H), 2.42(s,3H), 3.55(m,2H), 3.69(m,2H), 6.58(s,1H), 6.96(s,2H)
N(n-Pr)$_2$	Me	Me	H	0.90(t,6H), 1.65(m,4H), 1.90(s,3H), 2.30(s,3H), 2.40(s,3H), 2.45(s,3H), 3.5-3.6(m,4H), 6.55(s,1H), 6.93(s,2H)
N(CH$_2$CH=CH$_2$)$_2$	Me	Me	H	1.90(s,6H), 2.30(s,3H), 2.40(s,3H), 2.48(s,3H), 4.20(d,4H), 5.15-5.30(m,4H), 5.09-6.10(m,2H), 6.55(s,1H), 6.95(s,2H)
EtN(CH$_2$CH(CH$_3$)$_2$)	Me	Me	H	0.95(t,3H), 1.23(t,3H), 1.95(s,6H), 2.11(m,1H), 2.35(s,3H), 2.46(s,3H), 2.50(s,3H), 3.44(d,2H), 3.68(q,2H), 6.59(s,1H), 6.98(s,2H)
EtN(CH$_2$C(Me)=CH$_2$)	Me	Me	H	1.21(t,3H), 1.73(d,3H), 1.93(s,6H), 2.34(s,3H), 2.42(s,3H), 2.48(s,3H), 3.63(q,2H), 4.18(s,2H), 4.95(s,1H), 5.05(s,1H), 6.58(s,1H), 6.97(s,2H)
EtN(CH$_2$)$_2$N(CH$_3$)$_2$	Me	Me	H	1.26(t,3H), 1.88(s,6H), 2.31(s,3H), 2.34(s,6H), 2.41(s,3H), 2.43(s,3H), 2.62(m,2H), 3.64(q,2H), 3.74(m,2H), 6.55(s,1H), 6.94(s,2H)
EtN(CH$_2$C(Me)$_2$)	Me	Me	Me	0.91(d,6H), 1.17(t,3H), 1.84(s,6H), 1.95(s,3H), 2.05(m,1H), 2.35(s,3H), 2.38(s,3H), 2.47(s,3H), 3.36(d,2H), 3.61(q,2H), 6.98(s,2H)

B	R_3	R_4	R_6	^{1}H NMR ($CDCl_3$) δ (ppm)
NH-$CHEt_2$	Me	Me	Me	0.96(t,6H), 1.5-1.8(m,4H), 1.82(s,6H), 1.87(s,3H), 2.3(s,3H), 2.39(s,3H), 2.40(s,3H), 4.30(m,1H), 4.76(d,1H,NH), 6.94(s,2H)
NH-$CHEt_2$	Me	Me	H	0.98(t,6H), 1.5-1.8(m,4H), 1.92(s,6H), 2.32(s,3H), 2.45(s,3H), 2.46(s,3H), 4.32(m,1H), 4.82(d,1H,NH), 6.44(s,1H), 6.95(s,2H)
NHCH(n-$Pr)_2$	Me	Me	Me	0.94(s,6H), 1.3-1.7(m,4H), 1.84(s,6H), 1.89(s,3H), 2.32(s,3H), 2.39(s,3H), 2.41(s,3H), 4.46(s.1H), 4.73(s,1H,NH), 6.96(s,2H)
NHCH(Me)(n-Bu)	Me	Me	Me	0.92(t,3H), 1.27(d,3H), 1.37(m,4H), 1.5-1.7(m,2H), 1.83(s,6H), 1.84(s,3H), 1.89(s,3H), 2.33(s,3H), 2.40(s,3H), 2.43(s,3H), 4.41(m,1H), 4.77(d,1H,NH), 6.96(s,2H)
NH(n-Bu)	Me	Me	H	0.98(t,3H), 1.35-1.45(m,2H), 1.5-1.7(m,2H), 1.90(s,6H), 2.30(s,3H), 2.43(s,3H), 2.44(s,3H), 3.57(q,2H), 4.90(m,t,1H, NH), 6.38(s,1H), 6.93(s,2H)
NHEt	Me	Me	H	1.30(t,3H), 1.90(s,6H), 2.30(s,3H), 2.44(s,3H), 2.46(s,3H), 3.62(m,2H), 4.90(t,1H,NH), 6.40(s,1H), 6.93(s,2H)
NH-cyclopropyl	Me	Me	Me	0.57(m,2H), 0,85(m,2H), 1.81(s,6H), 1.87(s,3H), 2.31(s.3H), 2.34(s,3H), 2.48(s,3H), 3.00(m.1H), 5.17(s,1H), 6.95(s,2H)
NH-(R)-CH(Et)(CH_2OH)	Me	Me	Me	1.05(t,3H), 1.5-1.8(m,2H), 1.80(s,6H), 1.89(s,3H), 2.31(s.3H), 2.40(s,6H), 3.84(2sets of ABq. 2H), 3.96(m.1H), 5.14(d,1H.NH), 6.95(s.2H), 7.04(s,1H)
NHCH(Me)(Et)	Me	Me	Me	0.99(t.3H), 1.25(d,3H), 1.57(m.2H), 1.82(s.6H), 1.88(s.3H), 2.31(s.3H), 2.39(s,3H), 2.41(s,3H), 4.35(m.1H), 4.78(d.1H,NH), 6.94(s.2H)

B	R_3	R_4	R_5	^{1}H NMR ($CDCl_3$) δ (ppm)
NH-(S)-CH(Et)(CH_2OH)	Me	Me	Me	1.05(t,3H), 1.5-1.8(m,2H), 1.80(s,6H), 1.89(s,3H), 2.31(s,3H), 2.40(s,6H), 3.84(2sets of ABq, 2H), 3.96(m,1H), 5.14(d,1H,NH), 6.95(s,2H), 7.04(s,1H)
NH-cyclopentyl	Me	Me	Me	1.49(m,2H), 1.67(m,2H), 1.81(s,6H), 1.87(s,3H), 2.13(m,2H), 2.31(s,3H), 2.37(s,3H), 2.42(s,3H), 4.58(m,1H), 4.93(d,1H,NH), 6.94(S,2H)
NH-(S)-CH(Et)(CH_2OH)	Me	Me	H	1.08(t,3H), 1.5-1.8(m,2H), 1.89(s,6H), 2.30(s,3H), 2.43(s,3H), 2.448(s,3H), 2.453(s,3H), 3.86(2sts of ABq,2H), 3.98(m,1H), 5.17(d,1H,NH), 6.48(s,1H), 6.81(s,1H), 6.94(s,1H)
NH-(S)-CH(Et)(CH_2OMe)	Me	Me	H	0.98(t,3H), 1.6-1.8(m,2H), 1.90(s,3H), 1.91(s,3H), 2.30(s,3H), 2.42(s,3H), 2.44(s,3H), 3.39(s,3H), 3.53(2 sets of ABq,2H), 4.46(m,1H), 5.24(d,1H,NH), 6.42(s,1H), 6.92(s,2H)
NHCH(Me)(Et)	Me	Me	H	0.99(t,3H), 1.26(d,3H), 1.5-1.7(m,2H), 1.91(s,6H), 2.30(s,3H), 2.44(s,6H), 4.34(m,1H), 4.79(d,1H,NH), 6.42(s,1H), 6.93(s,2H)
NH-(R)-CH(Et)(CH_2OMe)	Me	Me	Me	1.00(t,3H), 1.55-1.8(m,2H), 1.82(s,6H), 1.87(s,3H), 2.31(s,3H), 2.38(s,3H), 2.39(s,3H), 3.39(s,3H), 3.54(m,2H), 4.45(m,1H), 5.25(d,1H,NH), 6.94(s,2H)
NH-(S)-CH(Et)(CH_2OMe)	Me	Me	Me	1.00(t,3H), 1.55-1.8(m,2H), 1.82(s,6H), 1.87(s,3H), 2.31(s,3H), 2.38(s,3H), 2.39(s,3H), 3.39(s,3H), 3.54(m,2H), 4.45(m,1H), 5.25(d,1H,NH), 6.94(s,2H)

B	R_3	R_4	R_6	^{1}H NMR ($CDCl_3$) δ (ppm)
NH-CH_2CH(Me)(Et)	Me	Me	Me	0.96(t,3H), 1.00(d,3H), 1.1-1.3(m,2H), 1.4-1.6(m,2H), 1.6-1.8(m,1H), 1.82(s,6H), 1.88(s,3H), 2.31(s,3H), 2.39(s,3H), 2.42(s,3H), 3.40(m,1H), 3.54(m,1H), 5.00(t,1H,NH), 6.94(s,2H)
NH-(S)-CH(CH_2Ph)(CH_2OH)	Me	Me	Me	1.77(s,3H), 1.78(s,3H), 1.82(s,3H), 1.99(s,3H), 2.30(s,3H), 2.41(s,3H), 2.84(m,1H), 3.12(m,1H), 3.75(m,1H), 3.93(m,1H), 4.27(m,1H), 5.15(d.1H,NH), 6.94(s,2H), 7.2-7.4(m,5H)
NH-(R)-CH(CH_2Ph)(CH_2OH)	Me	Me	Me	1.77(s,3H), 1.78(s,3H), 1.82(s,3H), 1.99(s,3H), 2.30(s,3H), 2.41(s.3H), 2.84(m,1H), 3.12(m,1H), 3.75(m,1H), 3.93(m,1H), 4.27(m,1H), 5.15(d,1H,NH), 6.94(s,2H), 7.2-7.4(m,5H)
NH-(S)-CH(CH_2Ph)(CH_2OMe)	Me	Me	Me	1.80(s,3H), 1.83(s,3H), 1.88(s,3H), 2.31(s,3H), 2.33(s,3H), 2.44(s,3H), 2.90(m,1H), 3.13(m,1H). 3.40(s,3H), 3.44(m,2H), 4.70(m,1H), 5.35(d,1H.NH), 6.95(s,2H), 7.2-7.4(m.5H)
NH-(R)-CH(CH_2Ph)(CH_2OMe)	Me	Me	Me	1.80(s,3H), 1.83(s.3H), 1.88(s.3H), 2.31(s,3H), 2.33(s,3H), 2.44(s,3H), 2.90(m,1H), 3.13(m.1H), 3.40(s,3H), 3.44(m,2H), 4.70(m,1H), 5.35(d,1H,NH), 6.95(s,2H), 7.2-7.4(m.5H)
NH-(S)-CH(Et)(CH_2OEt)	Me	Me	H	1.00(t,3H), 1.20(t.3H), 1.6-1.8(m,2H0, 1.90(s,3H), 1.91(s,3H), 2.30(s,3H), 2.42(s.3H). 2.43(s,3H), 3.4-3.6(m,2H), 4.41(m.1H), 5.34(d,1H,NH), 6.42(s,1H), 6.93(s,2H)
NHCH$_2$CH(n-Bu)(Et)	Me	Me	Me	0.89(t,3H), 0.95(t.3H), 1.2-1.4(m,7H), 1.54-1.62(m.1H), 1.82(s,6H). 1.88(s.3H). 2.31(s.3H), 2.39(s.3H). 2.42(s.3H). 3.53(m.2H). 4.90(m.1H). 6.95(s.2H



NR_1R_2	R_4	R_6	R_5
	^{1}H-NMR($CDCl_3$) δ (ppm)		
EtN(n-Bu)	Me	Me	2,4-dimethylphenyl
	0.89(t,3H), 1.15(t,3H), 1.30(m,2H), 1.2-1.4(m,2H), 1.87(s,3H), 1.97(s,3H), 2.33(s,3H), 2.37(s,3H), 2.44(s,3H), 3.49(t,2H), 3.55(q,2H), 6.9-7.2(m,3H)		
$N(n\text{-}Pr)_2$	Me	Me	2,4-dimethylphenyl
	0.86(t,6H), 1.62(m,4H), 1.87(s,3H), 1.97(s,3H), 2.34(s,3H), 2.37(s,3H), 3.48(m,4H), 6.95-7.20(m,3H)		
EtN(n-Bu)	Me	Me	2,6-dimethylphenyl
	0.89(t,3H), 1.31(t,3H), 1.31(m,2H), 1.62(m,2H), 1.86(s,3H), 1.90(s,3H), 2.35(s,3H), 2.43(s,3H), 3.50(t,2H), 3.56(q,2H), 7.1-7.2(m,3H)		
EtN(n-Pr)	Me	Me	2,4-dimethylphenyl
	0.89(t,3H), 1.18(t,3H), 1.66(m,2H), 1.86(s,6H), 1.91(s,3H), 2.35(s,3H), 2.43(s,3H), 3.43(m,2H), 3.56(m,2H), 7.0-7.2(m,3H)		
EtN(n-Bu)	Me	H	2,5-dimethylphenyl
	0.93(t,3H),1.22(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 2.04(s,6H), 2.33(s,3H), 2.41(s,3H), 2.42(s,3H), 3.58(t,2H), 3.64(q,2H), 6.70(s,1H), 7.06(s,1H), 7.1-7.25(m,2H)		
EtN(n-Bu)	Me	H	3-methyl-4-chlorophenyl
	0.94(t,3H), 1.23(t,3H), 1.23-1.45(m,2H), 1.4-1.6(m,2H), 2.43(s,3H), 2.44(s,3H), 2.58(s,3H), 3.4-3.75(m,4H), 6.94(s,1H), 7.4-7.65(m,3H)		
EtN(n-Bu)	Me	H	2,6-dimethyl-4-bromophenyl

NR_1R_2	R_4	R_5	R_6
	^{1}H-NMR($CDCl_3$) δ (ppm)		
	0.92(t,3H), 1.22(t,3H), 1.25-1.40(m,2H), 1.55-1.60(m,2H), 1.91(s,6H), 2.40(s,3H), 2.43(s,3H), 3.57(m,2H), 3.64(q,2H), 6.50(s,1H), 7.27(s,2H)		
EtN(n-Bu)	Me	H	2,4-dimethyl-6-bromophenyl
	0.98(t,3H), 1.28(T,3H), 1.3-1.5(m,2H), 1.6-1.8(M,2H), 2.00(s,3H), 2.36(s,3H), 2.48(s,3H), 2.53(s,3H), 3.64(t,2H), 3.71(q,2H), 6.63(s,1H), 7.09(d,1H), 7.38(d,1H)		
$NHCH(Et)_2$	Me	H	2,6-dimethyl-4-bromophenyl
	0.98(t.6H), 1.5-1.8(m,4H), 1.94(s,6H), 2.44(s.3H), 2.45(s,3H), 4.30(M,1H), 4.80(d,1H,NH), 6.39(S,1H), 7.28(s.2H)		
$NHCH(Et)(CH_2OH)$ (S)-isomer	Me	H	2,6-dimethyl-4-bromophenyl
	1.07(t,3H), 1.5-1.8(m,2H), 1.90(s,6H), 2.42(s,3H), 2.44(s,3H), 3.5-3.8(m,2H), 3.87(m,1H), 5.18(d,1H,NH), 6.45(s,1H), 6.56(s,1H), 7.27(s,2H)		
$NHCH(Et)(CH_2OMe)$	Me	H	2,6-dimethyl-4-bromophenyl
	1.00(t,3H), 1.55-1.75(m,2H), 1.92(s,6H), 2.42(s,3H), 2.43(s,3H), 3.39(s,3H), 3.55(2 sets of ABq,2H), 4.46(m,1H), 5.28(d,1H,NH), 6.38(s,1H), 7.26(s,2H)		
$NHCH(Et)(CH_2OH)$	Me	H	2,6-dimethyl-4-chlorophenyl
	1.07(t,3H), 1.55-1.80(m,2H), 1.91(s,6H), 2.42(s,3H), 2.45(s,3H), 3.74(2 sets of ABq,2H), 4.00(m,1H), 5.18(d,1H,NH), 6.46(s,1H), 6.60(brs,1H), 7.11(s,2H)		
$NH\text{-}CH(Et)(CH_2OH)$ (R)-isomer	Me	H	2.6-dimethyl-4-bromophenyl
	1.07(t,3H), 1.55-1.75(m,2H), 1.90(s,6H), 2.42(s,3H), 2.44(s,3H), 3.75(2 sets of ABq,2H), 4.00(m,1H), 5.14(d,1H,NH), 6.45(s,1H), 6.50(brs,1H), 7.27(s,2H)		

EXAMPLE 7

A. 1-[2-Amino-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-3-yl]-2-ethyl-butan-1-one

A mixtur of 3-hydroxy-2-butanone (0.637 g, 7.23 mmol), 2,4,6-trimethylaniline (0.973 g. 7.19 mmol) and p-toluenesulfonic acid (0.012 g. 0.06 mmol) in 15 ml c:

benzene was refluxed using a Dean-Stark trap to remove water. After 3 hours, 4-ethyl-3-oxo-hexanenitrile (1.008 g, 0.724 mmol) was added and the mixture was refluxed for an additional 15 hours until all the starting material was consumed. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was dried and concentrated to give 1.679 g of brown oil which was purified by silica gel column chromatography to give 368 mg of the title compound as a brown oil and 732 mg of undesired 2-(2-ethyl-butyl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrole-3-carbonitrile as a yellow solid. ^{1}H-NMR ($CDCl_3$) (the title compound) δ 0.94(t,6H), 1.4-1.8(m,4H), 1.73(s,3H), 1.98(s,6H), 2.25(s,3H). 2.34(s,3H), 3.00(m,1H), 5.80(brs,2H), 6.99(s,2H) ppm. ^{1}H-NMR ($CDCl_3$) (2-(2-ethyl-butyl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrole-3-carbonitrile)δ0.85(t,6H),1.5-1.85(m,4H). 1.71(s,3H), 1.88(s,6H), 1.95-2.10(m,1H), 2.14(s,3H), 2.34(s,3H), 6.96(s,2H) ppm.

B. N-[3-(2-ethyl-butyryl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide

A mixture of 1-[2-amino-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-3-yl]-2-ethyl-butan-1-one (326 mg, 1 mmol) and acetic anhydride (108 mg, 1.05 mmol) in 3 ml of acetic acid was heated to reflux for 2 hours. The mixture was cooled, quenched with water, neutralized with saturated potassium carbonate, and extracted with ethyl acetate. The organic layer was washed with brine, dried, and concentrated to give the title compound as a dark oil. The oil was purified through silica gel column chromatography to give 107 mg of the title compound as a brown oil. ^{1}H-NMR ($CDCl_3$) δ 0.88(t,6H), 1.4-1.8(m,4H), 1.76(s,3H), 1.88(s,3H), 1.93(s,6H), 2.25(s,3H). 2.28(s,3H), 2.98(m,1H), 6.89(s,2H) ppm.

C. 4-(1-Ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of N-[3-(2-ethyl-butyl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide (100 mg, 0.27 mmol), ammonium chloride (290 mg, 5.42 mmol), and acetamide (1.635 g) was heated to reflux for 2 hours. The mixture was cooled, quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 56 mg of the title compound as a dark oil. The oil was purified through silica gel column chromatography to give the title compound as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ 0.85(t,6H), 1.70-2.0(m,4H), 1.83(s,6H), 1.99(s,3H), 2.36(s,3H), 2.44(s,3H), 2.61(s,3H), 3.26(m,1H), 7.00(s,2H) ppm.

EXAMPLE 8

Butyl-ethyl-[2,5-dimethyl-7-(2,6-dimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidine-4-yl]amine and 4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3.5-dimethyl-benzoic acid

A solution of 7-(4-bromo-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-butyl-ethyl-amine (0.700 g, 1.63 mmol) in 5 ml of dry tetrahydrofuran (THF) was added to a cooled solution of n-butyl lithium (n-BuLi) (2.5 M in hexane, 1.79 mmol) in 5 ml of dry THF at -78°C and stirred at that temperature for 20 minutes.

A part (1 mL) was taken from the reaction mixture and was quenched with an excess of water and extracted with ethyl acetate, dried and concentrated to give butyl-ethyl-[2,5-dimethyl-7-(2,6-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]amine as a clear oil. The oil was treated with 1 N HCl in methanol and concentrated to dryness. The residue was recrystallized from ethyl acetate to give the corresponding HCl salt as white crystals, mp 148-150°C.

The rest of the reaction mixture was quenched with an excess of dry ice at -78°C and the -78°C bath was removed. After 30 minutes, tlc showed that no starting material was left, and the mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give an off-white solid (0.550 g). The solid was recrystallized from 2-propanol to give the second title compound as white crystals, mp 228-230°C.

EXAMPLE 9

4-[4-(Butyl-ethyl-amino)-2.5-dimethyl-pyrrolo[2.3-d]pyrimidin-7-yl]-3.5-dimethyl-benzoic acid methyl ester

A mixture of 4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-benzoic acid (0.230g, 0.583 mmol) in 40 ml of 1 N HCl and methanol was heated at reflux for 3 hours (tlc showed that all starting materials were consumed). The mixture was concentrated to dryness. The residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate. brine, dried and concentrated to give the title compound as a light brown oil. The oil was purified through silica gel column chromatography using 5% ethyl acetate in h xane as an luent to give a golden oil. The corresponding HCl salt was prepared as an off-white solid, mp 58-60°C.

EXAMPLE 10

[4-(Butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethylphenyl}-methanol

A solution of 4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-benzaldehyde (0.100 g, 0.264 mmol) in 1 ml MeOH was treated with sodium borohydride (0.030 g, 0.793 mmol) and stirred at room temperature for 20 minutes. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to dryness to give a clear oil. The oil was purified through silica gel column chromatography to give the title compound (0.092 g, 92% yield) as a white solid, mp 93-95°C.

EXAMPLE 11

Butyl-ethyl-[7-(4-fluoromethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-amine

A solution of {4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethylphenyl}-methanol (0.071 g, 0.186 mmol) in 2 ml anhydrous methylene chloride was cooled to -78°C and treated with dimethylaminosulfur trifluoride (0.063g, 0.390 mmol) and stirred at room temperature for 1 hour. The mixture was quenched with water and extracted with chloroform. The organic layer was washed with brine, dried, and concentrated to give an oil which was purified through silica gel using 2% methanol/chloroform as eluent to give the title compound as an off-white solid, mp 163-165°C.

EXAMPLE 12

Butyl-ethyl-[7-(4-methoxymethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-amine

A solution of {4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethylphenyl}-methanol (0.100 g, 0.263 mmol) in 1 ml of dry tetrahydrofuran was treated with sodium hydride (0.0116 g, 0.289 mmol, 60% in oil). After stirring for 10 minutes, an excess of methyl iodide was added. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give an oil. The oil was purified through silica gel column using 10% ethyl acetate in hexane as eluent to give 0.081 g (78%) of the title compound as a white glass form.

EXAMPLE 13

[7-(4-aminomethyl-2.6-dimethyl-phenyl)-2.5-dimethyl-7H-pyrrolo[2.3-d]pyrimidin-4-yl]-butyl-ethyl-amine

A solution of 4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-benzaldehyde (0.200 g, 0.528 mmol) in 2 ml of methanol was treated with sodium cyanoborohydride (0.023 g, 0.37 mmol), ammonium acetate (0.407 g, 5.28 mmol) and sodium sulfate. After stirring for 1 hour, the mixture was concentrated to remove methanol and the residue was dissolved in water, saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give an oil. The oil was purified through silica gel column using 10% methanol in chloroform as eluent to give the title compound as a clear oil. The corresponding di-HCl salt was prepared as a white solid, mp 158-160°C.

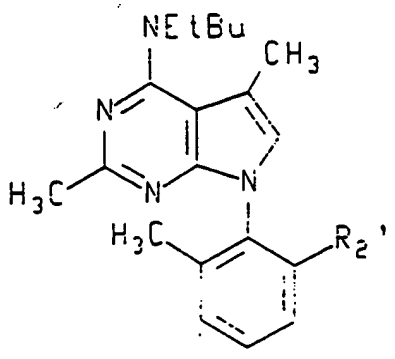
EXAMPLE 14

Butyl-ethyl-[7-(4-methoxyethyl-2.6-dimethyl-phenyl)-2.5-dimethyl-7H-pyrrolo[2.3-d]pyrimidin-4-yl]-amine

The title compound was prepared starting from the 1-{4-[4-(butyl-ethyl-amino)-2,5-dimethyl-pyrrolo[2,3-d]pyrimidin-7-yl]-3,5-dimethyl-phenyl}-ethanol, sodiumhydride and methyl iodide and employing the procedure of Example 12.

The ^{1}H NMR data of the compounds prepared by the methods of Examples 8 to 15 as well as other compounds prepared by these methods are listed in the following Table.

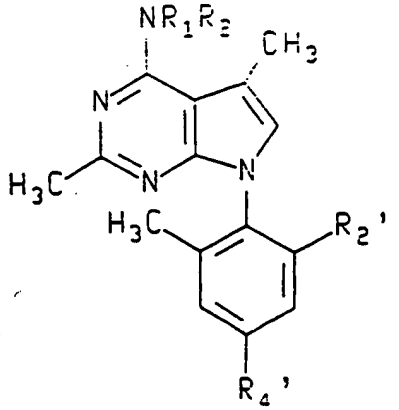
Table I



A

Example	R2'	R4'	^{1}H NMR ($CDCl_3$) δ (ppm)
8	Me	H	0.93(t,3H), 1.23(t,3H), 1.25-1.40(m,2H), 1.55-1.60(m,2H), 1.95(s,6H), 2.42(s,3H), 2.45(s,3H), 3.58(m,2H), 3.64(q,2H), 6.56(s,1H), 7.05-7.20(M,3H)
8	Me	COOH	0.95(t,3H), 1.27(t,3H), 1.3-1.45(m,2H), 1.6-1.8(m,2H), 1.96(s,6H), 2.43(s,3H), 2.56(s,3H), 3.65(t,2H), 3.72(q,2H), 6.61(s,1H), 7.52(s,2H)
	Me	CHO	0.92(t,3H), 1.23(t,3H), 1.25-1.40(m,2H), 1.55-1.70(m,2H), 2.03(s,6H), 2.42(s,3H), 2.43(s,3H), 3.58(m,2H), 3.64(q,2H), 6.54(s,1H), 7.65(s,2H), 9.99(s,1H)
10	Me	CH_2OH	0.92(t,3H), 1.22(t,3H), 1.25-1.40(m,2H), 1.55-1.70(m,2H), 1.94(s,6H), 2.41(s,3H), 2.45(s,3H), 3.58(t,2H), 3.65(q,2H), 4.55(s,2H), 6.54(s,1H), 7.09(s,2H)
	Me	CH(Me)(OH)	0.91(t,3H), 1.21(t,3H), 1.2-1.4(m,2H), 1.44(d,3H), 1.5-1.7(m,2H), 1.91(s,6H), 2.39(s,3H), 2.42(s,3H), 3.57(t,2H), 3.64(q,2H), 4.75(q,1H), 6.53(s,1H), 7.11(s,1H), 7.13(s,1H)
9	Me	COOMe	0.92(t,3H), 1.23(t,3H), 1.25-1.30(m,2H), 1.5-1.7(m,2H), 1.99(s,6H), 2.41(s,3H), 2.43(s,3H), 3.58(t,2H), 3.64(q,2H), 3.91(s,3H), 6.53(s,1H), 7.81(s,2H)
11	Me	CH_2F	0.90(t,3H), 1.20(t,3H), 1.24-1.40(m,2H), 1.5-1.7(m,2H), 1.95(s,6H), 2.38(s,3H), 2.42(s,3H), 3.54(t,2H), 3.62(q,2H), 4.30(d, 2H), 6.50(s,1H), 7.10(s,2H)
13	Me	CH_2NH_2	0.90(t,3H), 1.20(t,3H), 1.2-1.4(m,2H), 1.5-1.7(m,2H), 1.93(s,6H), 2.40(s,3H), 2.42(s,3H), 3.54(t,2H), 3.62(q,2H), 3.82(s,2H), 6.52(s,1H), 7.10(s,2H)
	Me	CONHMe	0.94(t,3H), 1.2-1.4(m,5H), 1.4-1.6(m,2H), 1.96(s,6H), 2.43(s,3H), 2.75(s,1.5H), 2.82(s,1.5H), 3.24(s,1H), 3.5-3.8(m,4H), 6.53(s,1H), 7.22(s,1H), 7.48(s,1H)
	Me	OH	0.89(t,3H), 1.20(t,3H), 1.2-1.4(m,2H), 1.5-1.7(m,2H), 1.76(s,6H), 2.379s,3H), 2.52(s,3H), 3.58(t,2H), 3.65(q,2H), 6.26(s,2H), 6.50(s,1H)

Example	R2'	R4'	^{1}H NMR ($CDCl_3$) δ (ppm)
	Me	I	0.92(t,3H), 1.22(t,3H), 1.2-1.35(m,2H), 1.5-1.7(m,2H), 1.89(s,6H), 2.40(s,3H), 2.44(s,3H), 3.57(t,2H), 3.64(q,2H), 6.50(s,1H), 7.48(s,2H)
	Me	Et	0.93(t,3H), 1.25(m,6H), 1.2-1.4(m,2H), 1.55-1.60(m,2H), 1.92(s,6H), 2.41(s,3H), 2.46(s,3H), 2.63(q,2H), 3.57(t,2H), 3.64(q,2H), 6.55(s,1H), 6.96(S,2H)
14	Me	CH(Me)(OMe)	0.88(t,3H), 1.18(t,3H), 1.2-1.4(m,2H), 1.38(d,3H), 1.5-1.7(m,2H), 1.90(s,6H), 2.36(s,3H), 2.40(s,3H), 3.24(s,3H), 3.4-3.65(m,4H), 4.20(q,1H), 6.50(s,1H), 7.00(s,2H)
12	Me	CH_2OMe	0.92(t,3H), 1.22(t,3H), 1.2-1.4(m,2H), 1.5-1.65(m,2H), 1.94(s6H), 2.41(s,3H), 2.44(s,3H), 3.42(s,3H), 3.45-3.52(m,4H), 4.42(s,2H), 6.53(s,1H), 7.10(s,2H)
	Me	$C(Me)_2(OH)$	0.92(t,3H), 1.22(t,3H), 1.25-1.40(m,2H), 1.5-1.7(m,2H), 1.58(s,6H), 1.95(s,6H), 2.40(s,3H), 2.45(s,3H), 3.5-3.7(m,4H), 6.54(s,1H), 7.23(s,2H)



NR1R2	R2'	R4'	^{1}H NMR ($CDCl_3$) δ (ppm)
$NHCH(Et)_2$	Me	H	0.98(t,6H), 1.5-1.8(m,4H), 1.97(s.6H), 2.44(s.3H), 2.46(s.3H), 4.34(m.1H), 4.81(d.1H), 6.44(s.1H), 7.1-7.2(m.3H)

$NHCH(Et)_2$	Me	CHO	0.98(t,6H), 1.5-1.8(m,4H), 2.06(s,6H), 2.43(s,3H), 2.46(s,3H), 4.31(m,1H), 4.83(d,1H), 6.43(s,1H), 7.66(s,1H), 9.99(s,1H)
$NHCH(Et)(CH_2OMe)$	Me	H	1.01(t,3H), 1.4-1.6(m,2H), 1.95(s,6H), 2.42(s,3H), 2.44(s,3H), 3.40(s,3H), 3.55(2 sets of ABq,2H), 4.48(m,1H), 5.26(d,1H,NH), 6.43(s,1H), 7.0-7.2(m,3H)

EXAMPLE 15

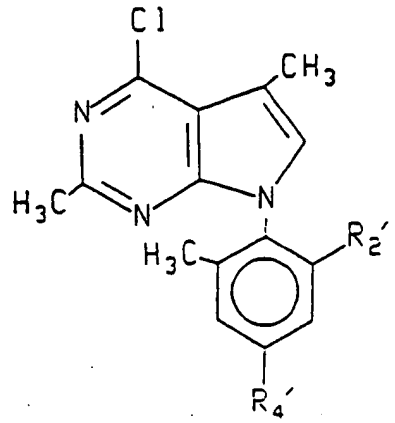
The following compounds of above formula A (Example 14) were prepared by procedures analogous to those in Examples 8 to 13.

R2'	R4'	^{1}H NMR ($CDCl_3$) δ (ppm)
H	Me	0.95(t,3H), 1.23(t,3H), 1.2-1.4(m,2H), 1.55-1.77(m,2H), 2.08(s,3H), 2.38(s,3H), 2.44(s,3H), 2.50(s,3H)3.59(t,2H), 3.66(q,2H), 6.71(ws,1H), 7.0-7.2(m,3H)
CHO	Me	0.95(t,3H), 1.26(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 2.05(s,3H), 2.438(s,3H), 2.443(s.3H), 2.448(s,3H), 3.5-3.8(m,4H), 6.7(s,1H), 7.39(d,1H), 7.68((d,1H), 9.33(s,1H)
CH_2OH	Me	0.96(t,3H), 1.27(t,3H), 1.25-1.45(m,2H), 1.6-1.75(m,2H), 1.95(s,3H), 2.41(s,3H), 2.43(s,3H), 2.44(s,3H), 3.5-3.8(m,4H), 4.15(m,2H), 6.6(s,1H), 7.11(s,1H), 7.26(s,1H)
CH_2F	Me	0.96(t,3H), 1.28(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.95(s,3H), 2.41(s,3H), 2.43(s,3H), 2.46(s,3H), 3.5-3.8(m,4H), 5.01(2 sets of ABq,2H), 6.63(s,1H), 7.15(s,1H), 7.25(s,1H)
CH(Me)(OH)	Me	0.96(t,3H), 1.27(t,3H), 1.25-1.409m,2H), 1.43(d,3H), 1.6-1.8(m,2H), 1.93(s,3H), 2.42(s,6H), 2.45(s,3H), 3.4-3.8(m,4H), 4.37(q,2H), 5.10(s,1H), 6.62(s,1H), 7.09(s,1H), 7.35(s,1H

R2'	R4'	^{1}H NMR ($CDCl_3$) δ (ppm)
I	Me	0.96(t,3H), 1.27(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.97(s,3H), 2.34(s,3H), 2.46(s,3H), 2.50(s,3H), 3.5-3.8(m,4H), 6.58(s,1H), 7.10(S,1H), 7.62(s,1H)
Cl	Me	0.95(t,3H), 1.25(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.97(s,3H), 2.36(s,3H), 2.44(s,3H), 2.48(s,3H), 3.5-3.8(m,4H), 6.61(s,1H), 7.04(s,1H), 7.19(s,1H)
$C(Me)_2(OH)$	Me	0.94(t,3H), 1.18(s,3H), 1.25(t,3H), 1.25-1.5(m,2H), 1.55(s,3H), 1.6-1.8(m,2H), 1.69(s,3H), 2.38(s,3H), 2.42(s,3H), 2.43(s,3H), 3.5-3.8(m,4H), 4.13(brs,1H), 6.57(s,1H), 7.04(s,1H), 7.39(s,1H)
CH_2NH_2	Me	0.96(t,3H), 1.26(t,3H), 1.3-1.5(m,2H), 1.6-1.8(M,2H), 1.85(s,3H), 2.28(S<3H), 2.38(s,6H), 3.28(q,2H), 3.5-3.8(m,4H), 6.58(s,1H), 6.93(s,1H), 6.99(s,1H)
CH_2OMe	Me	0.96(t,3H), 1.26(t,3H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.92(s,3H), 2.38(s,3H), 2.44(s,3H), 2.46(s,3H), 3.25(s,3H), 3.61(t,2H), 3.68(q,2H), 4.04(ABq,2H), 6.62(s,1H), 7.06(s,1H), 7.22(s,1H)
Et	Me	0.95(t,3H), 1.04(t,3H), 1.26(t,3H), 1.25-1.45(m,2H), 1.90(s,3H), 2.15-2.35(m,2H), 2.37(s,3H), 2.44(s,3H), 2.47(s,3H), 3.63(m,2H), 3.67(q,2H), 6.57(s,1H), 6.98(s,1H), 7.01(s,1H)
CH(Me)(OMe)	Me	0.96(t,3H), 1.2-1.4(m,6H), 1.25-1.45(m,2H), 1.6-1.8(m,2H), 1.91(s,3H), 2.41(s,3H), 2.43(s,3H), 2.44(s,3H), 3.14(s,3H), 3.5-3.75(m,4H), 3.81(q,1H), 6.54(s,1H), 7.06(s,1H), 7.25(s,1H)

Example 16

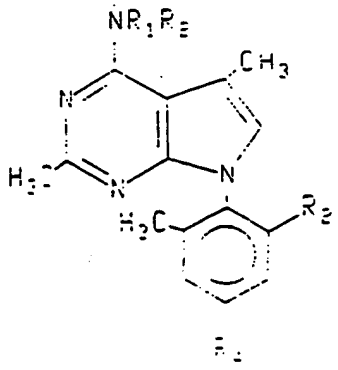
A. The following compounds were prepared by the procedures analogous to those in Examples 8 to 13 starting from n-BuLi with 4-chloro-2,5-dimethyl-7-(2,6-dimethyl-4-bromo- or 2,4-dimethyl-6-bromo-phenyl)-7H-pyrrolo-[2,3-d]pyrimidine, followed by quenching with an appropriate electrophile compound.



$R^{2'}$	$R^{4'}$	^1H NMR ($CDCl_3$) δ (ppm)
Me	Et	1.25(t,3H), 1.89(s,6H), 2.50(s,3H). 2.63(s,3H), 2.62(m,2H), 6.78(s,1H). 6.99(s,2H)
Me	OH	1.79(s,6H), 2.50(s,3H), 2.74(s,3H). 6.36(s,2H), 6.80(s,1H), 8.60(s,1H)
Me	$C(Me_2)(OH)$	1.60(s,6H), 1.93(s,6H), 2.50(s,3H), 2.63(s,3H), 6.78(s,1H), 7.23(s,1H)
CH_2F	Me	1.92(s,3H), 2.43(s,3H), 2.52(s,3H). 2.53(s,3H), 4.87(ABq,1H), 5.11(ABq,1H), 6.87(s,1H), 7.26(s,1H), 7.27(s,1H)
Et	Me	1.01(t,3H), 1.87(s,3H), 2.20(q,2H), 2.38(s,3H), 2.53(s,3H), 2.65(s,3H). 6.81(s,1H), 7.01(s,1H). 7.04(s,1H)
$C(Me_2)(OH)$	Me	1.26(s,3H), 1.43(s,3H), 1.66(s,3H). 2.40(s,3H), 2.52(s,3H), 2.62(s,3H). 6.83(s,1H), 7.07(s,1H), 7.45(s,1H)
H	Me	2.04(s,3H), 2.40(s,3H), 2.51(s,3H). 2.67(s,3H). 6.92(s,1H). 7.13(s,2H) 7.18(s,1H)

$R^{2'}$	$R^{4'}$	^{1}H NMR ($CDCl_3$) δ (ppm)
CHO	Me	2.00(s,3H), 2.47(s,3H), 2.54(s,3H), 2.63(s,3H), 6.92(s,1H), 7.45(m,1H), 7.70(m,1H), 9.39(s,1H)
CH_2OH	Me	1.88(s,3H), 2.36(s,3H), 2.50(s,3H), 2.57(s,3H), 3.56(brs,1H), 4.05-4.25(m,2H), 6.84(s,1H), 7.08(s,1H), 7.25(s,1H)

B. The following compounds were prepared starting with the appropriate amine and the appropriate 4-chloro-2,5-dimethyl-7-(substituted phenyl)-7H-pyrrolo[2,3-d]pyrimidine (compounds listed in the table above under 16A or other related compounds) in DMSO and employing the general procedure of Example 5.



NR_1R_2	R_2'	R_4'	^{1}H NMR ($CDCl_3$) δ (ppm)
NH-(S)-CH(Et)(CH_2OH)	Me	Et	1.07(t,3H), 1.23(t,3H), 1.45-1.56(m,2H), 1.90(s,3H), 1.91(s,3H), 2.43(s,3H), 2.45(s,3H), 2.60(q,2H), 3.65(m,1H), 3.83(m,1H), 4.00(m,1H), 5.17(d,1H), 6.49(s,1H), 6.95(s,2H)
NH-(S)-CH(Et)(CH_2OH)	Et	Me	1.00(t,3H), 1.07(t,3H), 1.6-1.85(m,2H), 1.88(s,3H), 2.15-2.30(m,2H), 2.32(s,3H), 2.42(s,3H), 2.48(s,3H), 3.6-3.9(m,2H), 3.92-4.10(m,1H),5.25(d,1H), 6.5(s,1H), 6.94(s,1H), 7.0(s,1H)

NR_1R_2	R_2'	R_4'	^1H NMR ($CDCl_3$) δ (ppm)
NH-(S)-CH(Et)(CH_2OH)	Me	CMe_2OH	1.08(t,3H), 1.58(s,6H), 1.6-1.9(m,2H), 1.94(s,3H), 1.95(s,3H), 2.46(s,3H), 2.50(s,3H), 3.5-3.95(m,2H), 4.2(brs ,1H), 5.28(brs,1H), 6.53(s,1H), 7.24(s,2H)
NH-(S)-CH(Et)(CH_2OH)	C(OH)(Me_2)	Me	1.11(t,3H), 1.24(s,3H), 1.5-1.9(m,2H), 1.50(s,0.5x3H), 1.53(0.5x3H), 1.71(s,3H), 2.39(s,3H), 2.43(s,3H), 2.48(s,3H), 3.16(brs.0.5H), 3.29(brs,0.5H), 3.6-3.95(m,2H), 3.95-4.10(m,1H), 5.2-5.3(m,1H), 6.54(s,1H), 7.05(s,1H), 7.40(s,0.5H), 7.43(s,0.5H)
NH-(S)-CH(Et)(CH_2OH)	H	Me	1.10(t,3H), 1.5-1.9(m,2H), 2.05(s,3H), 2.37(s,3H), 2.48(s,6H), 3.6-3.9(m,2H), 3.9-4.1(m,1H), 5.23(d,1H), 6.64(s.1H), 7.0-7.2(m,2H)
NH-(S)-CH(Et)(CH_2OH)	CHO	Me	1.09(t,3H), 1.55-1.90(m,2H), 2.02(s,3H), 2.42(s,6H), 2.47(s,3H), 3.6-3.9(m,2H), 4.0-4.15(m,1H), 5.27(t,1H), 6.62(s,1H), 7.39(s,1H), 7.65(s,1H), 9.36(s,1H)
NH-(S)-CH(Et)(CH_2OH)	CH_2OH	Me	both diastereoisomers were separated by column chromatography and showed identical spectra. 1.11(t,3H), 1.55-1.90(m,2H), 1.95(s,3H), 2.40(s,3H), 2.43(s,3H), 2.49(s,3H), 3.6-3.95(m,2H), 4.0-4.3(m,2H), 4.4(brs,1H), 5.30(d,1H), 6.57(s,1H), 7.11(s,1H), 7.27(s,1H)
NH-(S)-CH(Et)(CH_2OH)	CH_2F	Me	1.11(t,3H), 1.5-1.85(m,2H), 1.94(s,3H), 2.41(s,3H), 2.45(s,3H), 2.47(s,3H), 3.6-3.9(m,2H), 4.0-4.2(m,1H), 4.75-5.25(m,2H), 5.24(m,1H), 6.58(s,1H), 7.16(s,1H), 7.24(s,1H)

Example 17

The following compounds were pr pared by the procedures analogous to those in Examples 8 to 13 starting from an excess of n-BuLi with 4-substituted amino-2,5-dimethyl-7-(2,4,6-tri-substituted-phenyl)-7H-pyrrolo-[2.3-d]pyrimidine. followed by quenching with an appropriate electrophile.

NR_1R_2	R_2'	R_2'	^1H NMR ($CDCl_3$) δ
NH-(S)-CH(Et)(CH_2OH)	CH_2CH_2OH	Me	1.11(t,3H), 1.5-1.9(m,2H), 1.84(s.3H), 2.37(s,3H), 2.45(s,3H), 2.48(s,3H), 2.45-2.65(m,2H), 3.6-3.95(m,4H), 4.15(m,1H), 5.28(d,1H), 6.54(s,1H), 7.02(s,1H), 7.09(s,1H)
NH-(S)-CH(Et)(CH_2OH)	Me	CHO	1.08(t,3H), 1.5-1.8(m,2H), 2.02(s,6H), 2.42(s,3H), 2.46(s,3H), 3.6-3.9(m,2H), 4.0(brs,1H), 5.20(d,1H), 6.49(s,1H), 7.65(s,2H), 9.98(s,1H)
NH-(S)-CH(Et)(CH_2OH)	Me	I	1.06(t,3H), 1.6-1.9(m,2H), 1.88(s.6H), 2.42(s,3H), 2.44(s,3H), 3.6-3.9(m,2H), 4.08(brs,1H), 5.20(d.1H), 6.45(s,1H), 7.48(s,2H)
NH-(S)-CH(Et)(CH_2OH)	Me	CH_2OH	1.08(t,3H), 1.6-1.85(m,2H), 1.93(s,6H), 2.45(s,6H), 3.6-3.95(m,2H), 4.10(brs,1H), 4.60(s.2H), 5.24(brs,1H), 6.50(s,1H), 7.11(s.2H)
NH-(S)-CH(Et)(CH_2OH)	Me	C(Me)-($C=CH_2$)	1.08(t,3H), 1.5-1.8(m,2H), 1.94(s.6H), 2.13(s,3H), 2.44(s,3H), 2.45(s.3H), 3.55-3.90(m,2H), 4.00(brs,1H), 5.07(s,1H), 5.20(d,1H), 5.35(s.1H), 6.50(s,1H), 7.21(s,2H)

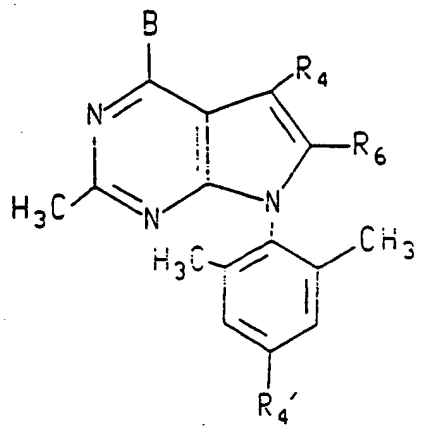
EXAMPLE 18

4-sec-Butoxy-1-(2,5,6-trimethylphenyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine

Sodium hydride (0.114g, 4.77mmol, 60% in oil) was washed with hexane, then treated with 2-butanol (1.18g, 15.90 mmol). After 20 minutes, a mixture of 4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine(0.500g,1.59mmol) in 5 ml of anhydrous tetrahydrofuran was added to the reaction mixture and stirred for 2 hours. The mixture was concentrated to dryness, dissolved in ethyl acetate and water. The organic layer was separated, washed with brine, dried, and concentrated to give a clear oil. The oil residue was purified through silica gel column chromatography using 20% ethyl acetate in hexane as eluent to give a clear oil which crystallized und r high vacuo to give 0.450 g (80.5%) of an off-whit solid. The solid was recrystallized from i-propanol to give gold crystals, mp 178-180°C.

EXAMPLE 19

The following compounds were prepared starting with the appropriate alcohol or thiol and 4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine or 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine and employing the general procedure of Example 18.



B	R_4'	R_5	R_6	^{1}H NMR ($CDCl_3$) δ (ppm)
$OCHEt_2$	Me	Me	Me	0.99(t,6H), 1.74(m,4H), 1.84(s.6H), 1.92(s,3H), 2.34(s,3H), 2.37(s.3H), 2.48(s,3H), 5.34(m,1H), 6.98(s.2H)
$OCHMe_2$	Me	Me	Me	1.41(d.6H), 1.82(s,6H), 1.91(s.3H), 2.33(s,3H), 2.36(s,3H), 2.48(s.3H), 5.55(m,1H), 6.98(s,2H)
OCH(Me)(Et)	Me	Me	Me	1.02(t,3H), 1.28(d,3H), 1.65-1.80(m,2H), 1.83(s,6H), 1.92(s.3H), 2.33(s,3H), 2.37(s,3H), 2.48(s.3H), 5.38(m,1H), 6.98(s,2H)
OCH(Et)(n-Pr)	Me	Me	Me	0.94(t,3H), 0.97(t,3H), 1.38-1.60(m,2H), 1.6-1.8(m,4H), 1.82(s,6H), 1.90(s,3H), 2.32(s.3H), 2.35(S,3H), 2.46(s,3H), 6.96(s.2H)
OCH(Et)(n-Bu)	Me	Me	Me	0.90(t,3H), 0.99(t,3H), 1.3-1.5(m.4H), 1.6-1.8(m,4H), 1.832(s.3H), 1.837(s,3H), 1.92(s.3H), 2.34(s.3H), 2.36(s,3H), 2.48(s.3H), 5.39(m.1H), 6.98(s.2H)

B	R_4'	R_4	R_6	^1H NMR ($CDCl_3$) δ (ppm)
OCH(Et)(n-pentyl)	Me	Me	Me	0.88(t,3H), 0.98(t,3H), 1.4-1.6(m,6H), 1.6-1.8(m,4H), 1.82(s,6H), 1.90(s,3H), 2.32(s,3H), 2.36(s,3H), 2.47(s,3H), 5.40(m,1H), 6.96(s,2H)
OCH(Et)(n-hexyl)	Me	Me	Me	0.85(t,3H), 0.97(t,3H), 1.20-1.50(m,8H), 1.6-1.8(m,4H), 1.82(s,6H), 1.90(s,3H), 2.32(s,3H), 2.35(s,3H), 2.46(s,3H), 5.37(m,1H), 6.96(s,2H)
$OCH(n\text{-}Pr)_3$	Me	Me	Me	0.94(t,3H), 1.4-1.6(m,4H), 1.6-1.8(m,4H), 1.83(s,6H). 1.91(s,3H), 2.33(s,3H), 2.36(S,3H), 2.48(s.3H), 5.50(m,1H), 6.97(s.2H)
$OCH(Et)(CH_2OMe)$	Me	Me	Me	1.03(t,3H), 1.82(s,3H), 1.83(s,3H), 1.91(s,3H), 2.33(s,3H), 2.37(s,3H), 2.47(s,3H), 3.43(s,3H), 3.68(m,2H), 5.55(m,1H), 6.97(s.2H)
$OCHEt_2$	Me	Me	H	0.99(t,6H), 1.63(m,4H), 1.92(s,6H), 2.32(s,3H), 2.41(s,3H), 2.50(s,3H), 5.35(m,1H), 6.52(s.1H), 6.96(s,2H)
$OCH(Et)(CH_2OMe)$	Me	Me	H	1.00(t,3H), 1.6-1.8(m.2H), 1.86(s,3H), 1.87(s,3H), 2.28(s.3H), 2.40(s.3H), 2.489s,3H), 3.40(s.3H), 3.62(m,2H), 5.51(m,1H), 6.48(s.1H). 6.92(s.2H)
OCH_2-(S)-$CH(NH_2)(Et)$	Br	Me	H	1.03(t,3H), 1.3-1.5(m.2H), 1.91(s,6H), 2.42(s,3H), 2.51(s,3H). 4.13(m,1H), 4.26(m,1H), 4.44(m.1H), 6.52(s,1H), 7.29(s,2H)
S-CH(Me)-CH(OH)(Me)	Br	Me	H	1.25(d,3H), 1.41(d,3H), 1.87(s,3H), 1.89(s,3H), 2.50(s.3H), 2.55(s,3H), 4.1-4.3(m,2H), 6.63(s.1H), 6.65(brs,1H), 7.30(s.2H)

EXAMPLE 20

A. 2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile

A mixture of 4-chloro-2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine (10.000 g. 31.90 mmol) and potassium cyanide (20.75 g. 319 mmol) in 100

ml dimethylsulfoxide was heated at 130°C oil bath over weekend. The mixtur was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to give 9.61 g (99%) of brown soild. The solid was recrystallized from i-propanol to give 6.34 g (65%) of the title compound as light golden crystals, mp 188-190°C. ^{1}H NMR ($CDCl_3$) δ 1.8(s,6H), 2.07(s,3H), 2.36(s,3H), 2.50(s,3H), 2.65(s,3H), 7.00(s,2H).

B. 2-Methyl-1-[2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-butan-1-one

To a solution of sec-butyl magnesium chloride (1.5 ml, 3.0 mmol, 2 M in diethyl ether) in 24 ml of dry tetrahydrofuran was added 2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile (0.814 g, 2.67 mmol) at room temperature and stirred for 5 hours. The mixture was quenched with 5 ml of 2N HCl, neutralized with saturated sodium bicarbonate, extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow solid. The solid was purified through silica gel column chromatography using chloroform as eluent to give 0.884 g (90%) of the title compound as yellow crystals, mp 133-135°C.

EXAMPLE 21

[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one and 1-[2,5,6-Trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan-1-one were prepared starting from 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile, and ethyl magnesium chloride and n-BuLi, respectively, employing the general procedure of Example 20B.

EXAMPLE 22

[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-ol

A solution of 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one (0.300 g, 0.89 mmol) in 10 ml of methanol was treated with sodium borohydride ($NaBH_4$) (0.169 g, 4.47 mmol) at room temperature and stirred for 15 minutes. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried, and concentrated to give 0.291 g (96%) of the title compound as light yellow crystals. The crystals were recrystallized from i-propanol to give light yellow crystals, mp 143-144°C.

EXAMPLE 23

The following compounds were prepared by reduction of the corresponding ketone derivative with $NaBH_4$ by the procedure described in the Example 22:

1-[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan1-ol; and

2-Methyl-1-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-butan-ol.

EXAMPLE 24

The following compounds were prepared by reaction of the corresponding alcohol derivative with NaH, followed by reacting with alkyl iodide using the procedure analogous to that described in Example 12:

4-(1-Methoxy-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidine;

4-(1-Ethoxy-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine; and

4-(1-Methoxy-2-methyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine.

EXAMPLE 25

[2,5,6-Trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan-3-ol

A solution of 1-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidin-4-yl]-propan-1-one (0.220 g, 0.656 mmol) in 10 ml of dry THF was treated with ethyl magnesium bromide (0.787 mmol, 0.39 ml, 2.0 m in THF) at 0°C and stirred at room temperature for 1 hour. The mixture was quenched with diluted HCl, neutralized with aqueous NaOH and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow solid. The solid was redcrystallized from ethyl ether/ethyl acetate to give off-white crystals. mp 164-166.5°C.

EXAMPLE 26

[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-hexan-3-ol

The title compound was prepared by reacting 1-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidin-4-yl]-propan-1-one with n-propyl magnesium chloride using the procedure described in Example 25.

EXAMPLE 27

(1-Ethyl-1-fluoro-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

The title compound was prepared by reacting of 3-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan-3-ol with dimethylaminosulfur trifluoride using the procedure described in Example 11.

EXAMPLE 28

(1-Ethyl-propenyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of 3-[2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pentan-3-ol (0.041 g, 0.122 mmol), concentrated sulfuric acid (0.055 g, 0.56 mmol) and acetic acid (0.136 g, 2.27 mmol) was heated to reflux for 1 hour. cooled, diluted with water, basified to pH 10 with 2 N NaOH and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to dryness to give 43 mg of the title compound as a clear oil. The oil was purified through silica gel column chromatography to give 40 mg of the title compound as a white solid, mp 59-61°C.

EXAMPLE 29

Compounds listed in the following Table II in which B is CH(OAc)(CHMeEt) and a mixture of two isomers 4-(1-ethyl-butenyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine and 4-(1-n-propyl-propenyl)-2,5,6-trimethyl-7-(2,4,6-trimethyl-phenyl)-7H-pyrrolo[2,3-d]pyrimidine [see Table II in which B is C(=CHEt)(Et) and C(=CHMe)(n-Pr)] were prepared by a procedure analogous to that described in Example 28.

EXAMPLE 30

(1-Ethyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of two isomers, 4-(1-ethyl-butenyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine and 4-(1-n-propyl-propenyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine (67 mg, 0.185 mmol) in ethyl acetate (18 ml) and 10% Pd/C (38 mg) was hydrogenated at 50 psi for 15 hours. The mixtur was filter d through celite. The filtrated was washed with brine, dried and concentrated to give 119 mg of oil. The oil was purified through siiica gel column

chromatography using 7% ethyl acetate in hexane as eluent to give 31 mg (46%) of the title compound as off-white crystals, mp 100-102°C.

EXAMPLE 31

[-2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-pr pan-1-one oxime

A mixture of 1-[-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one (0.598 g, 1.783 mmol), hydroxylamino hydrochloride (0.370 g, 5.35 mmol), sodium acetate (0.439 g, 5.35 mmol) in MeOH (30 ml) was stirred at room temperature for 24 hours. The mixture was concentrated to dryness. The residue was diluted with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 0.657 g of a white glass form. The glass form was purified through silica gel column chromatography to separated both E (white crystals, mp 162-164°C, confirmed by X-ray structural analysis) and Z (white crystals, mp 84-87°C) isomers and a mixture of E and Z isomers (mp-150-190°C).

EXAMPLE 32

1-[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propylamine

Hydrogenation of 1-[-2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-propan-1-one oxime with 10% Pd/C in MeOH using the general procedure described in Example 28 resulted in the title compound.

EXAMPLE 33

[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylmethyl]-formamide

A mixture of 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile (1.000 g, 3.29 mmol), 1:1 Al/Ni alloy (1.0 g) in 70% aqueous formic acid (10 ml) was stirred at room temperature for 1 hour. The mixture was filtered through Celite, washed with 100 ml of water and 100 ml of ethyl acetate. The organic layer was separated, dried and concentrated to give a light green oil. The oil was purified through silica gel column chromatography using 2% methanol in chloroform as eluent to give 0.960 g (86.5%) of the title compound as an off-white soild. Tne solid was recrystallized from thyl acetate to give a light yellow crystals, mp 202-204°C.

EXAMPLE 34

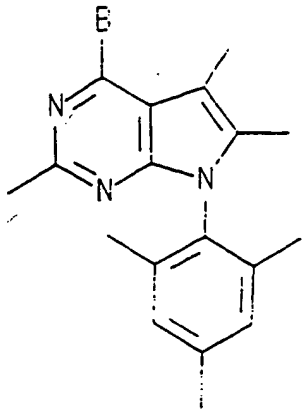
N-[2,5,6-Trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylmethyl]-acetamide

A mixture of 2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carbonitrile (0.500 g, 1.64 mmol) and 10% Pd/C (0.500 g) in ethanol was hydrogenated at 55 psi for 5 hours. The mixture was filtered through celite and the filtrate was concentrated to give 0.500g (98.8%) of N-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylmethyl]-amine.

A mixture of N-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylmethyl]-amine (0.200 g, 0.648 mmol), acetic anhydride (0.132 g, 1.30 mmol), triethylamine (0.132 g, 1.30 mmol) in anhydrous methylene chloride (1 ml) was stirred at room temperature for 1 hour. The mixture was quenched with water and extracted with methylene chloride. The organic layer was separated, dried and concentrated to give 0.217 g (95.6%) of the title compound as a light tan solid. The solid was purified through silica gel column chromatography using 5% methanol in chloroform as eluent to give 0.200 g (88.1%) of the title compound as golden crystals. mp 140-143°C.

The ^{1}H NMR data of the compounds which are described in the Examples 20 to 34 are listed in the following Table.

Table II



B	^{1}H NMR ($CDCl_3$) δ (ppm)
CO-(n-Bu)	1.00(t,3H), 1.4-1.6(m,2H), 1.7-1.9(m,2H), 1.83(s,6H), 2.06(s,3H), 2.34(s,3H), 2.35(s,3H), 2.38(s,3H), 3.27(t,2H), 7.03(s,2H)
COEt	1.26(t,3H), 1.81(s,6H), 2.04(s,3H), 2.32(s,3H), 2.36(s,3H), 2.68(s,3H), 3.27(q,2H), 7.00(s,2H)
CO-CH(Me)(Et)	0.99(t,3H), 1.24(d,3H), 1.45-1.65(m,1H), 1.7-1.9(m,1H), 1.83(s,6H), 2.05(s,3H), 2.30(s,3H), 2.37(s,3H), 2.68(s,3H), 3.91(m,1H0, 7.03(s.2H)
CH(OH)(n-Bu)	0.95(t,3H), 1.2-1.8(m,6H), 1.77(s,3H), 1.87(s,3H), 2.00(s,3H), 2.37(s,3H), 2.39(s,3H), 2.63(s,3H), 5.20(dd,1H), 7.02(s.2H)
CH(OH)(Et)	1.12(t,3H), 1.6-2.0(m,2H), 1.77(s,3H), 1.87(s,3H), 2.00(s,3H), 2.37(s,3H), 2.39(s.3H). 2.63(s,3H), 4.97(d,1H), 5.15(m,1H), 7.02(s.2H)
CH(OMe)(Et)	1.02(t,3H), 1.82(s,3H), 1.83(s,3H), 2.01(s,3H), 1.8-2.1(m,2H), 2.36(s,3H), 2.45(s,3H), 2.669s,3H), 3.359s,3H0, 4.68(t,1H), 7.01(s.2H)
CH(OEt)(Et)	1.02(t,3H), 1.22(t,3H), 1.82(s,3H), 1.83(s,3H), 1.7-2.1(m,2H), 2.36(s.3H), 2.46(s,3H), 2.65(s.3H), 3.49(m,2H), 4.75(t,1H), 7.01(s.2H)
CH(OMe)(CHMeEt)	0.68(d,1.8H), 0.83(t,1.2H), 0.95(t,1.8H), 1.10(d,1.2H), 1.1-1.5(m.2H), 1.9-2.2(m,1H). 1.8(3 sets of s,6H), 2.0(s,3H), 2.359s,3H0 2.53(s.3H0. 2.65(s,3H), 3.25(s.1.8H), 3.30(s.1.2H), 4.42(d.0.6H), 4.5(d,0.4H), 7.0(s.2H)
CH(OAc)(CHMeEt)	0.7(d,1.5H), 0.85(t,1.5H), 0.94(t,1.5H), 1.1(d,1.5H), 1.1-1.5(m,2H), 1.81(s,1.5H), 1.83(s,3H), 1.869s,1.5H), 2.0(s,3H), 2.22(s,1.5H), 2.24(s,1.5H), 2.2-2.4(m,0.5H), 2.32(s,3H), 2.49(s,1.5H), 2.51(s,1.5H), 2.60(s,3H), 3.0-3.2(m.0.5H), 6.12(m,1H). 7.0(s.2H)
$CFEt_2$	0.90(t,6H). 1.83(s,6H), 2.03(s,3H), 2.0-2.4(m.4H). 2.38(s.6H). 2.59(s,3H). 7.02(s.2H)
$CEt_2(OH)$	071(t.6H), 1.79(s,6H). 2.02(s,3H), 2.0-2.4(m.4H). 2.36(s,3H). 2.47(s.3H), 2.61(s.3H). 7.01(s.2H)

B	^{1}H NMR ($CDCl_3$) δ (ppm)
C(Et)(n-Pr)(OH)	0.71(t,3H), 0.84(t,3H), 1.4-1.6(m,2H). 1.80(s,3H), 1.81(s,3H), 2.04(s,3H), 1.9-2.2(m,4H), 2.38(s,3H), 2.49(s,3H), 2.63(s,3H), 6.83(s,1H), 7.03(s,2H)
CH(Et)(NH-n-Pr)	0.87(t,3H), 0.90(t,3H), 1.5-1.7(m,2H), 1.80(s,3H), 1.83(s,3H), 2.00(s,3H), 1.9-2.2(m,2H), 2.36(s,3H), 2.41(s,3H), 2.42(s,3H), 2.3-2.5(m,1H), 2.7-2.9(m,1H), 4.48(m.1H), 7.019s,2H), 7.15(s,1H),
=NOH)(Et)	1.0-1.2(m,3H), 1.79(s,1.5H), 1.80(s,1.5H), 1.99(s,1,.5H), 2.00(s,1.5H). 2.22(s,3H0, 2.35(s,3H), 2.65(s,1.5H), 2.68(s,1.5H) 2.7(q,1H), 2.99(q,1H), 6.93(s.2H), 9.05(brs.1H)
CH(Et)(NH2)	1.04(t,3H), 1.79(s,3H), 1.85(s,3H), 1.7-2.0(m,2H), 1.99(s,3H), 2.36(s,3H), 2.42(s,3H), 2.62(s,3H), 4.52(m,1H), 7.01(s,2H)
=CHMe)(Et)	1.00(t,2.1H), 1.1(t,0.9H), 1.47(d,0.9H), 1.82(s,6H), 1.9(d,2.1H), 2.02(s,3H), 2.25(s.3H), 2.4-2.8(m,5H), 5.6-5.8(m,1H), 7.0(s.2H)
=CHEt)(Et) + C(=CHMe)(n-Pr)	(m,5.4H), 1.82(s,6H), 1.869d,1.8H). 2.0(s.3H). 2.20(s,.1.2H), 2.21(s,1.8H), 2.359s.3H). 2.60(s,1.8H), 2.61(s,1.2H). 2.3-2.8(m.2.8H).5.4-5.8(m,1H). 6.959s.2H)
CH(n-Bu)(Et)	0.83(t.3H), 0.88(t,3H), 1.1-1.49(m.2H). 1.6-2.2(m.4H), 1.82(s.3H), 1.83(s.3H). 1.98(s.3H). 2.35(s,3H), 2.43(s,3H), 2.61(s,3H), 3.33(m.1H), 7.00(s.2H)
CH2NHCHO	1.79(s.6H), 2.00(s,3H), 2.35(s.3H), 2.48(s.3H), 2.62(s,3H), 4.98(d,2H), 7.01(s,2H), 8.05(brs,1H), 8.38(s,1H)
CH2NHCOCH3	1.79(s.6H), 1.97(s,3H), 2.12(s,3H), 2.34(s,3H), 2.43(s.3H), 2.61(s,3H), 4.90(d,2H). 6.99(s.2H), 7.46(brs.1H)

Example 35

A. 1-[2-Amino-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-3-yl]-2-ethyl-butan-1-one

A mixture of 3-hydroxy-2-butanone (0.637 g, 7.23 mmol), 2,4,6-trimethylaniline (0.973 g, 0.719 mmol) and p-toluene sulfonic acid (0.012 g) in 15 ml of benzen was heated at reflux under Dean-Stark trap for 3 hours. A solution of $(Et)_2CHCOCH_2CN$ (1.008 g, 7.24 mmol) was added to the reaction mixture and heated at reflux overnight. The mixture was cooled and diluted with ethyl acetate and water. The organic lay r was separated and washed with water, aqueous sodium carbonate, and then brine; dried and concentrated to give a brown oil which contains the desired compound. 0.368 g of the desired compound was isolated after silica gel column chromatography using chloroform as eluent. ^1H NMR ($CDCl_3$) δ 0.94 (t,6H), 1.5-1.8 (m,4H), 1.73 (s,3H), 1.98 (s,6H), 2.26 (s,3H), 2.34 (s,3H), 3.00 (m,1H), 5.78 (brs,2H), 6.99 (s,2H) ppm.

B. N-[3-(2-Ethyl-butyryl)-4,5-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrrol-2-yl]-acetamide

A mixture of the title compound from Example 35A (0.326 g, 1 mmol) and acetic anhydride (0.108 g, 1.05 mmol) in acetic acid (3 ml) was heated at reflux for 2 hours. The mixture was concentrated to dryness, diluted with water and extracted with ethyl acetate. The organic layer was washed with aqueous sodium carbonate and brine. dried and concentrated to give a dark oil. The oil was purified by silica gel column chromatography to give 107 mg of the title compound as a brown oil. ^1H NMR ($CDCl_3$) δ 0.88 (t,6H), 1.6-1.8 (m,4H), 1.76 (s,3H), 1.88 (s,3H), 1.93 (s,6H), 2.25 (s.3H), 2.28 (s,3H), 2.90-3.00 (m,1H), 6.89 (s,2H) ppm.

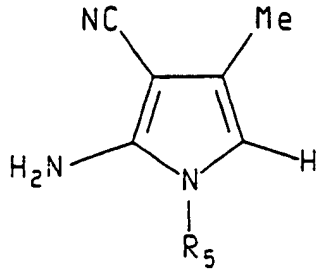
C. 4-(1-Ethylpropyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine

A mixture of the title compound of Example 35B (100 mg. 0.27 mmol) and ammonium chloride in 1.6 g of acetamide was heated at reflux for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the desired product which was purified by silica gel column chromatography to give the title compound as a yellow oil. ^1H NMR ($CDCl_3$) δ 0.85 (t,6H), 1.7-2.0 (m,4H), 1.83 (s,6H), 1.99 (s,3H), 2.35 (s,3H), 2.44 (s.3H), 2.61 (s.3H), 3.25-3.35 (m,1H), 7.00 (s,2H) ppm.

The following Preparations illustrate the synthesis of int rmediates.

Preparation 1

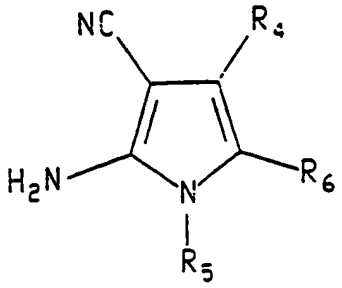
The following compounds were prepared starting from the appropriate aniline and employing the general procedure of Example 1A.



R_5	^{1}H-NMR($CDCl_3$) δ (ppm)
3,5-ditrifluoromethylphenyl	2.2(s,3H), 4.0(s,2H), 6.15(s,1H), 7.9(s,2H)
2,5-dimethylphenyl	2.04(s,3H), 2.12(s,3H), 2.35(s,3H), 3.85(s,2H), 5.90(s,1H), 7.0(s,1H), 7.10-7.25(m,2H)
2-methyl-4-iodophenyl	2.05(s,3H), 2.10(s,3H), 3.80(s,2H), 5.85(s,1H), 6.92(d,1H), 7.60(dd,1H), 7.70(d,1H)
3-methyl-4-chlorophenyl	2.10(s,3H), 2.40(s,3H), 4.03(s,2H), 6.03(s,1H), 7.10(dd,1H), 7.21(d,1H), 7.45(d,1H)
4-bromo-2,6-dimethylphenyl	2.01(s,6H), 2.10(s,3H), 3.70(brs,2H), 5.72(s,1H), 7.30(s,2H)
2-bromo-4,6-dimethylphenyl	2.06(s,3H), 2.13(s,3H), 2.35(s,3H), 3.83(brs,2H), 5.81(s,1H), 7.08(s,1H), 7.35(s,3H)
4-chloro-2,6-dimethylphenyl	2.01(s,6H), 2.10(s,3H), 3.75(brs,2H), 5.75(s,1H), 7.14(s,2H)

Preparation 2

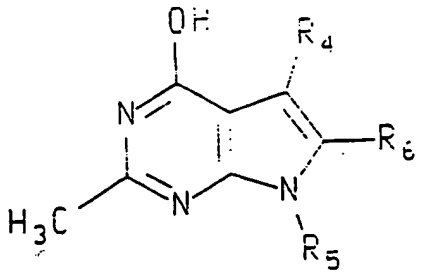
The following compounds were prepared starting from 3-hydroxy-2-butanone or 4-hydroxy-3-hexanone and the appropriate aniline and employing the general procedure of Example 2A.



R_4 and R_6	R_5	^{1}H-NMR($CDCl_3$) δ (ppm)
Me	2,4-dimethylphenyl	1.70(s,3H), 1.95(s,3H), 2.05(s,3H), 2.38(s,3H), 3.7(s,2H), 6.95-7.20(m,3H)
Me	2,6-dimethylphenyl	1.67(s,3H), 1.98(s,6H), 2.05(s,3H), 2.90(brs,2H), 7.05-7.21(m,3H)
Et	2,4,6-trimethylphenyl	No purification, the material was used directly for the next reaction step

Preparation 3

The following compounds were prepared starting from the corresponding compounds of preparations 1 and 2 and employing the general procedures of Examples 1B and 1C.

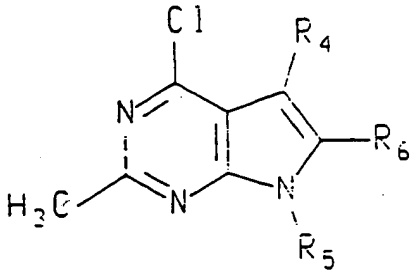


R_4=Me, R_5=H	^{1}H-NMR (solvent) δ (ppm)
R_5=3,5-ditrifluoromethylphenyl	(DMSO-d6) 2.32(s,3H), 7.50(s,1H), 8.05(s,1H), 8.55(s,1H), 12.10(s,1H)
R_5=2,5-dimethylphenyl	($CDCl_3$) 2.04(s,3H), 2.35(s,3H), 2.467(s,3H), 2.470(s,3H), 6.57(s,1H), 7.0-7.3(m,3H), 12.08(s,3H)

R_5=3-methyl-4-chlorophenyl	(DMSO-d_6) 2.29(s,3H), 2.31(s.3H), 2.38(s,3H), 7.12(s,1H), 7.55(m.2H), 7.67(d,1H), 11.90(s,1H)
R_5=4-bromo-2,6-dimethylphenyl	($CDCl_3$) 1.94(s,6H), 2.40(s,3H), 2.45(s,3H), 6.39(s,1H), 7.29(s.2H)
R_5=2-bromo-4,6-dimethylphenyl	(DMSO-d_6) 1.91(s,3H), 2.20(s.3H), 2.32(s,3H), 2.34(s,3H), 6.68(s.1H), 7.21(s,1H), 7.44(s,1H),11.80(s.1H)
R_5 = 4-chloro-2,6-dimethylphenyl	($CDCl_3$) 1.91(s,6H), 2.38(s,3H), 2.40(s,3H), 6.34(s,1H), 7.08(s.2H)
R_4 & R_6 = Me	^{1}H-NMR (solvent) δ (ppm)
R_5=2,4,6-trimethylphenyl	($CDCl_3$) 1.85(s,6H), 1.87(s,3H), 2.34(s,3H), 2.41(s,3H), 2.44(s.3H), 7.00(s,2H), 12.2(s,1H)
R_5=2,4-dimethylphenyl	($CDCl_3$) 1.90(s,3H), 1.93(s,3H), 2.38(s,3H), 2.42(s,6H), 7.0-7.2(m,3H), 12.25(s,1H)
R_5=2,6-dimethylphenyl	($CDCl_3$) 1.80-1.90(m,9H), 2.39(s,3H), 2.49(s,3H), 7.04-7.20(m,3H), 12.2(s.1H)

Preparation 4

The following compounds were prepared starting from the corresponding compounds of Preparation 3 and employing the general procedure in Example 1D.

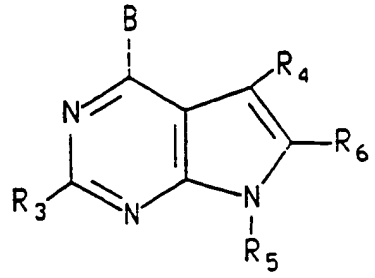


R_4=Me, R_6=H	^{1}H-NMR ($CDCl_3$) δ (ppm)
R_5=3,5-ditrifluoromethylphenyl	2.53(s.3H), 2.74(s,3H), 7.27(s.1H), 7.82(s,1H), 8.29(s.2H)

R_5=2,5-dimethylphenyl	2.01(s,3H), 2.35(s,3H), 2.50(s,3H), 2.66(s,3H), 6.91(s,1H), 7.05(s,1H), 7.10-7.30(m2H)
R_5=3-methyl-4-chlorophenyl	2.46(s,3H), 2.51(s,3H), 2.74(s,3H), 7.15(s,1H), 7.47(s,2H), 7.55(s,1H)
R_5=4-bromo-2,6-dimethylphenyl	1.89(s,6H), 2.49(s,3H), 2.62(s,3H), 6.75(s,1H), 7.32(s,2H)
R_5 = 2-bromo-4,6-dimethylphenyl	1.96(s,3H), 2.37(s,3H), 2.52(s,3H), 2.65(s,3H), 6.82(s,1H), 7.11(s,1H), 7.38(s,1H)
R_4 and R_6 = Me	^{1}H-NMR ($CDCl_3$) δ (ppm)
R_5=2,4,6-trimethylphenyl	1.81(s,6H), 1.99(s,3H), 2.35(s,3H), 2.46(s,3H), 2.59(s,3H), 7.01(s,2H)
R_5=2,4-dimethylphenyl	1.84(s,3H), 2.03(s,3H), 2.39(s,3H), 2.44(s,3H), 2.59(s,3H), 6.90-7.15(m,3H)
R_5=2,6-dimethylphenyl	1.83(s,6H), 1.98(s,3H), 2.45(s,3H), 2.58(s,3H), 7.10-7.30(m,3H)
R_5=4-chloro-2,6-dimethylphenyl	1.91(s,6H), 2.51(s,3H), 2.64(s,3H), 6.77(s,1H), 7.17(s,2H)
R_4 and R_6 = Et	^{1}H-NMR ($CDCl_3$) δ (ppm)
R_5=2,4,6-trimethylphenyl	0.96(t,3H), 1.31(t,3H), 1.85(s,6H), 2.38(s,6H), 2.46(q,2H), 2.62(s,3H), 2.92(q,2H), 7.02(s,2H)

CLAIMS

1. A compound of the formula



I

and the pharmaceutically acceptable acid addition salts thereof, wherein

B is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_8 alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, O-C -(C_1-C_6 alkyl), O-C NH(C_1-C_4 alkyl), O-C -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_8 alkyl), N(C_1-C_4alkyl)C (C_1-C_4 alkyl), NHC (C_1-C_4 alkyl), COOH, C O(C_1-C_4 alkyl), C NH(C_1-C_4 alkyl), C N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_8 alkyl may contain one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_8 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_2 alkyl, or one of hydroxy, bromo, iodo, C_1-

C_6 alkoxy, O-C(=O)-(C_1-C_6 alkyl), O-C(=O)-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, $NH(C_1$-C_2 alkyl), $N(C_1$-C_2 alkyl) (C_1-C_4 alkyl), N(C_1-C_4 alkyl)-C(=O)(C_1-C_4 alkyl), NHC(=O)(C_1-C_4 alkyl), COOH, C(=O)O(C_1-C_4 alkyl), C(=O)NH(C_1-C_4 alkyl), C(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a saturated 3- to 8-membered carbocyclic ring of which the 5- to 8-membered ring may contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_5 alkyl may contain one double or triple bond and may be substituted by from 1 to 3 substituents R_5 independently selected from the group consisting of hydroxy, C_1-C_3 alkoxy, fluoro, chloro or C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, $NH(C_1$-C_6 alkyl), N(C_1-C_6 alkyl)(C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, NHC(=O)(C_1-C_4 alkyl), $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), C(=O)O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidin-

piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, $NH(C_1$-C_4 alkyl), $N(C_1$-$C_4)(C_1$-C_2 alkyl), $COO(C_1$-C_4 alkyl), $CO(C_1$-C_4 alkyl), $SO_2NH(C_1$-C_4 alkyl), $SO_2N(C_1$-C_4 alkyl)$(C_1$-C_2 alkyl), SO_2NH_2, $NHSO_2(C_1$-C_4 alkyl), $S(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, C_1-C_4 alkoxy, amino, methylamino, dimethylamino or acetyl wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain one double or triple bond; with the proviso that R_5 is not unsubstituted phenyl:

R_6 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl$)(C_1$-C_2 alkyl), $SO_n(C_1$-C_6 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, $NHC(=O)(C_1$-C_4 alkyl), $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl$)(C_1$-C_2 alkyl), $C(=O)O(C_1$-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_{11} is hydrogen, hydroxy, fluoro, chloro, $COO(C_1$-C_2 alkyl), cyano, or $CO(C_1$-C_2 alkyl); and

R_{12} is hydrogen or C_1-C_4 alkyl; with the proviso that (1) B is not straight chain C_1-C_{12} alkyl, (2) when R_5 is unsubstituted cycloakyl, R_3 and R_4 are hydrogen, and R_6 is hydrogen or methyl, then B is not NHR_2 wherein R_2 is benzyl or thienylmethyl, and (3) when R_5 is p-bromophenyl, and R_3, R_4 and R_5 are methyl, then B not methylamino or hydroxyethylamino.

2. A compound according to claim 1 wherein B is NR_1R_2, $NHCHR_1R_2$, or $OCHR_1R_2$, wherein R_1 is C_1-C_5 alkyl, which may be substituted by one of hydroxy, fluoro or C_1-C_2 alkoxy, and may contain one double or triple bond, and R_2 is benzyl or C_1-C_5 alkyl which may contain one double or triple bond, wherein said C_1-C_5 alkyl or the phenyl in said benzyl may be substituted by fluoro, C_1-C_5 alkyl, or C_1-C_5 alkoxy.

3. A compound according to claim 1 wherein B is $CR_1R_2R_{11}$, wherein R_1 is C_1-C_6 alkyl which may be substituted by one C_1-C_6 alkoxy or hydroxy, R_2 is benzyl or C_1-C_6 alkyl wherein said C_1-C_6 alkyl or the phenyl in said benzyl may be substituted by one C_1-C_6 alkyl, C_1-C_6 alkoxy, fluoro, chloro or bromo, and R_{11} is hydrogen or fluoro.

4. A compound according to claim 1 wherein B is as defined in claim 1 and R_2 is C_1-C_6 alkyl which may be substituted by fluoro, C_1-C_6 alkyl or C_1-C_6 alkoxy and may contain one double or triple bond.

5. A compound according to claim 1 wherein B is as defined in claim 1 and R_2 is benzyl or methylthienyl, the phenyl or thienyl of which may be substituted by fluoro, chloro, C_1-C_4 alkyl or C_1-C_4 alkoxy.

6. A compound according to any one of claims 1 to 5 wherein R_3 is methyl, ethyl, fluoro, chloro, or methoxy.

7. A compound according to any one of claims 1 to 6 wherein R_4 and R_5 are hydrogen, methyl or ethyl.

8. A compound according to any one of claims 1 to 7 wherein R_6 is phenyl substituted by two or three substituents.

9. A compound according to claim 8 wherein said substituent is independently fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl, C_1-C_6 alkyl which may be substituted by one of hydroxy, C_1-C_4 alkoxy or fluoro and may have one double or triple bond, -(C_1-C_4 alkylene)O(C_1-C_2 alkyl), C_1-C_3 hydroxyalkyl, hydroxy, formyl, COO(C_1-C_2 alkyl), -(C_1-C_2 alkylene)amino, or -C(O)(C_1-C_4 alkyl).

10. A compound according to claim 1 wherein said compound is

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidin-4-yl]amine;

di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidin-4-yl]amine;

ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidin-4-yl]amine;

diethyl-2.5-dimethyl-7-(2.4.6-trimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidin-4-yl]amine;

n-butyl-ethyl-[2,5,6-trimethyl-7-(2.4.6-trimethylphenyl)-7H-pyrrolo[2.3-d]pyrimidin-4-yl]amine;

2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;

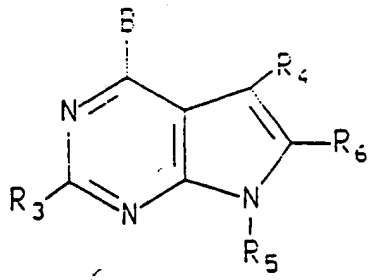
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;

n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;

2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine; or

2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol.

11. A pharmaceutical composition for the treatment of (a) illnesses induced or facilitated by corticotropin releasing factor or (b) inflammatory disorders such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache; pain; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurogenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; and fertility problems. which comprises a compound of the formula



I

and the pharmaceutically acceptable acid addition salts thereof, wherein

B is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_8 alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, O-C -(C_1-C_8 alkyl), O-C NH(C_1-C_8 alkyl), O-C -N(C_1-C_8

O O O

alkyl)(C_1-C_2 alkyl), amin , NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_6 alkyl), N(C_1-C_4alkyl)C (C_1-C_4 alkyl), NHC (C_1-C_4 alkyl), COOH, C O(C_1-C_4 alkyl), C NH(C_1-C_4 alkyl), C N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R_2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, O-C -(C_1-C_6 alkyl), O-C -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl) (C_1-C_4 alkyl), N(C_1-C_2 alkyl)-C (C_1-C_4 alkyl), NHC (C_1-C_2 alkyl), COOH, C O(C_1-C_4 alkyl), C NH(C_1-C_4 alkyl), C N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a saturated 3- to 8-membered carbocyclic ring, the 5- to 8-membered rings of which may contain one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_2 alkyl, benzyl or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_2 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_2 alkyl), SO(C_1-C_2 alkyl), or SO_2(C_1-C_2 alkyl), wherein said C_1-C_2 alkyl and C_1-C_6 alkyl may contain one

double or tripl bond and may be substituted by from 1 to 3 substituents R_6 independently selected from the group consisting of hydroxy, C_1-C_3 alkoxy, fluoro, chloro or C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_2 alkyl), $SO_n(C_1$-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, NHC (C_1-C_4 alkyl), $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), C O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or phenylmethyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, $NH(C_1$-C_4 alkyl), $N(C_1$-$C_4)(C_1$-C_2 alkyl), $COO(C_1$-C_4 alkyl), $CO(C_1$-C_4 alkyl), $SO_2NH(C_1$-C_4 alkyl), $SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2(C_1$-C_4 alkyl), $S(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, C_1-C_4 alkoxy, amino, methylamino, dimethylamino or acetyl wherein said C_1-C_4 alkyl and said C_1-C_6 alkyl may contain one double or triple bond; with the proviso that R_5 is not unsubtituted phenyl;

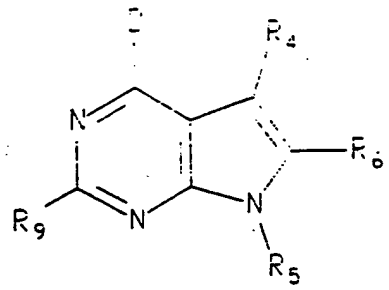
R_6 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)(C_1-C_2 alkyl), $SO_n(C_1$-C_6 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one hydroxy, trifluoromethyl, amino, carboxy, amido, NHC (C_1-C_4 alkyl), $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), C O(C_1-C_4 alkyl),

$N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), C O$(C_1\text{-}C_4$ alkyl), $C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_{11} is hydrogen, hydroxy, fluoro, chloro, $COO(C_1\text{-}C_2$ alkyl), cyano, or $CO(C_1\text{-}C_2$ alkyl); and

R_{12} is hydrogen or $C_1\text{-}C_4$ alkyl, in an amount effective in the treatment of said illnesses, and a pharmaceutically acceptable carrier.

12. A compound of the formula



wherein

D is hydroxy, chloro, or cyano;

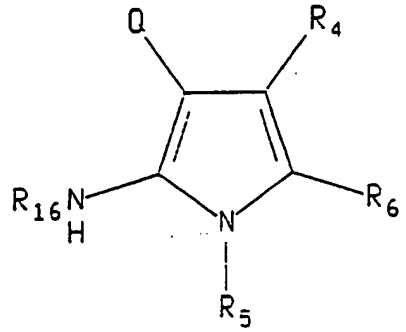
R_4 and R_6 are each independently hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1\text{-}C_6$ alkoxy, $SO_n(C_1\text{-}C_5$ alkyl), wherein n is 0, 1 or 2, or cyano, wherein said $C_1\text{-}C_6$ alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, $NHC(O)(C_1\text{-}C_4$ alkyl), $NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $C(O)O(C_1\text{-}C_4$ alkyl), $C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperdinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one to three of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ alkanoyl, phenyl or benzyl, wherein each of the above groups may be substituted independently by from one to three of fluoro, chloro, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy or trifluoromethyl, or one of hydroxy, bromo, iodo, cyano, nitro, amino, $NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_2)(C_1\text{-}C_2$ alkyl), $COO(C_1\text{-}C_2$ alkyl), $CO(C_1\text{-}C_2$ alkyl),

$SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), SO_2NH_2, $NHSO_2(C_1\text{-}C_4)$, $S(C_1\text{-}C_6$ alkyl), $SO_2(C_1\text{-}C_6$ alkyl), wherein said $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl may be substitut d by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl; and

R_9 is hydrogen, $C_1\text{-}C_6$ alkyl or chloro; with the proviso that when (a) R_4 and R_6 are methyl, R_9 is hydrogen and D is hydroxy, then R_5 is not phenyl (1) substituted by one of halogen, nitro, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, or trifluoromethyl, and optionally in addition substituted by one or two of halogen, $C_1\text{-}C_6$ alkyl or $C_1\text{-}C_6$ alkoxy, or (2) di-or trisubstituted by one of nitro or trifluoromethyl and one or two of halogen, $C_1\text{-}C_6$ alkyl or $C_1\text{-}C_6$ alkoxy, and (b) when D is chloro, R_4 and R_9 are hydrogen, and R_5 is $C_1\text{-}C_6$ alkyl, then R_5 is not unsubstituted cyclohexyl.

13. A compound of the formula



VII

wherein

Q is $C(O)CHR_1R_2$ or cyano;

R_1 is hydrogen, or $C_1\text{-}C_5$ alkyl which may be substituted by one or two substituents R_7 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, $C_1\text{-}C_8$ alkoxy, or nitro, and said $C_1\text{-}C_5$ alkyl may contain one or two double or triple bonds;

R_2 is $C_1\text{-}C_{12}$ alkyl, aryl or ($C_1\text{-}C_{10}$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl, or b nzoxazolyl; 3- to 8-membered cycloalkyl or ($C_1\text{-}C_6$ alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, benzyl or $C_1\text{-}C_4$ alkanoyl, wherein R_2 may be substituted independently by

from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, nitro, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds;

R_4 and R_6 are each independently hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, or SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, or cyano, wherein said C_1-C_6 alkyl may be substituted by one C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, piperidinyl, piperazinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, bromo, iodo, cyano, nitro, amino, NH(C_1-C_4 alkyl), N(C_1-C_4)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl; and

R_{16} is hydrogen or C(O)C_1-C_6 alkyl; with the proviso that when Q is cyano, R_4 and R_6 are not both methyl.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 93/10715

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D487/04 A61K31/505 C07D207/34 //(C07D487/04,239:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,31 45 287 (TROPONWERKE) 19 May 1983 cited in the application see page 4, line 1 - line 5; claim 1 ---	1,11
X	EP,A,0 475 411 (MARION MERRELL DOW) 18 March 1992 see claim 1 -----	12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
9 March 1994	23. 03. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 93/10715

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-A-3145287	19-05-83	NONE		
EP-A-0475411	18-03-92	AU-A-	8372991	19-03-92
		CA-A-	2051012	15-03-92
		CN-A-	1059909	01-04-92
		JP-A-	4270282	25-09-92
		NZ-A-	239750	25-02-94
		US-A-	5244896	14-09-93